Drug Class Review
on
Proton Pump Inhibitors

UPDATED FINAL REPORT

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TABLE OF CONTENTS

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INTRODUCTION

Proton pump inhibitors (PPIs) reduce stomach acid. PPIs act by blocking the enzyme system responsible for active transport of acid into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H(+)/K(+) ATPase) of the gastric parietal cell, also known as the "proton pump." Omeprazole, the first drug in this class, was introduced in 1988. Since then, four other PPIs have been introduced: lansoprazole (1995), rabeprazole (1999), pantoprazole (2000) and esomeprazole (2001). At the time of this report, no new PPIs have been approved by the FDA.

PPIs are used to treat peptic ulcers (duodenal and gastric), gastroesophageal reflux disease (GERD), and drug-induced ulcers (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]). For peptic ulcer disease, PPIs are given with antibiotics to eradicate H. pylori, the bacteria that causes ulcers. For gastroesophageal reflux, which causes heartburn and acid regurgitation, the American Gastroenterology Association recommends that patients first try lifestyle modifications and over-the-counter medicines. Lifestyle modifications include avoiding foods, beverages, and medicines that can aggravate heartburn, decreasing the size of portions at mealtimes, avoiding tight-fitting clothing, losing weight if overweight, and eating at least 3 hours before going to sleep. Over-the-counter medications include antacids and histamine-2 receptor antagonists (H2-RAs, commonly called "H2-blockers"), such as cimetidine or ranitidine. If these lifestyle changes and over-the-counter medications do not completely control heartburn symptoms, PPIs or high doses of H2-RAs may be prescribed. Many clinicians use H2-RAs as the initial therapy for gastroesophageal reflux. Current Oregon Health Plan policy is that PPIs be used primarily in patients who have inflammation of the esophagus (esophagitis). Even though use of H2-RAs is higher (36,130 claims vs 15,829 claims from 1/1/01 to 6/30/01), usage of the PPIs in the Oregon Health Plan is also significant (see Table 1).

Table 1. OHP fee-for-service sector PPIs (1/1/01 – 6/30/01)

Brand Name	Generic Name	Total Paid	Claim Count	Avg. Paid / Claim
PRILOSEC	OMEPRAZOLE	$717,403	5,750	$124.77
PREVACID	LANSOPRAZOLE	$697,084	5,919	$117.77
PROTONIX	PANTOPRAZOLE	$261,058	3,112	$83.89
ACIPHEX	RABEPRAZOLE	$92,154	848	$108.67
NEXIUM	ESOMEPRAZOLE	$23,384	200	$116.92

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different PPIs. The Oregon Evidence-based Practice Center developed the scope of the review by writing preliminary key questions, identifying the populations, interventions, and outcomes of interest and based on these, the eligibility criteria for studies. These were reviewed by the Oregon Health Resources Commission subcommittee for anti-ulcer therapies, comprised of local experts (pharmacists, primary care clinicians, and gastroenterologists), in public meetings and refined based on their input. In consultation with the subcommittee, we selected the following key questions to guide this review:

1. What is the comparative efficacy of different PPIs in adult patients with symptoms of GERD?

    a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in adult patients with symptoms of GERD?

    b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?

Comment. Usually, evidence-based reports emphasize health outcomes, which are events or conditions patients can feel or experience. Heartburn, waking at night, acid regurgitation, and quality of life are examples of health outcomes.

In addition to symptoms, the subcommittee specified endoscopic healing (or endoscopic recurrence) of esophagitis as an outcome measure for this key question. The severity of symptoms is not a reliable indicator of the presence of esophagitis; to diagnose it, it is necessary to perform endoscopy (direct visualization of the lining of the esophagus). Esophagitis appears as a tear, break, or ulceration in the lining of the esophagus. Endoscopic healing is generally defined as complete re-epithelialization of the ulcer crater(s).

Endoscopic healing is an indicator (also called an intermediate outcome measure), not a health outcome, because patients do not directly feel or experience esophagitis. While there is a general relationship between the degree of esophagitis and the severity of symptoms, patients who have no esophagitis can experience severe heartburn, and some patients who have esophagitis do not have symptoms.

Whenever judgments about efficacy are based on an intermediate measure, it is important to ask how strongly it is related to actual health outcomes. Over many years, esophagitis can lead scarring and narrowing of the esophagus (stricture) or to a condition called Barretts esophagus, which is a risk factor for esophageal cancer. Ideally, an evidence-based review would be able to compare PPIs based on how well long-term use prevented these complications. However, there are no data on the comparative efficacy of different PPIs to prevent long-term complications. In most studies of PPIs, patients who have esophagitis before treatment undergo another endoscopy four or eight weeks after beginning treatment to assess healing. There is no evidence that rates of esophageal healing after 4 or 8 weeks of treatment are associated with the

risk of stricture or esophageal cancer in the long run. As distinct from symptom relief, the benefit of quicker esophageal healing is also uncertain.

2. What is the comparative efficacy of different proton pump inhibitors in adult patients with peptic ulcer and NSAID-induced ulcer?

    a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?

    b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?

    c. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?

    d. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?

    e. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with NSAID-induced ulcer?

    f. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with NSAID-induced ulcer?

    g. In head-to-head comparisons, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

    h. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

    i. In head-to-head comparisons, what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?

    j. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?

Comment. In the short term, symptom relief and function are important health outcomes of an episode of ulcer disease. In the long run, the most important determinant of functional status and quality of life is the prevention of symptomatic recurrences and relapses of ulcers and of their complications (bleeding, hospitalization, and death). Studies of PPIs for ulcer disease are too short-term to address these outcomes directly. Instead they report two intermediate outcome measures. In the past the most commonly used indicator (intermediate outcome

measure) for the efficacy of ulcer treatment was "endoscopic healing," which means that, on repeat endoscopy after treatment, the ulcer is gone. Ulcer disease tends to recur even when the initial ulcer is completely healed. For this reason, endoscopic healing, while it is important as a predictor of relapse, was an imperfect indicator of long-term morbidity from ulcer disease. Since the discovery that H. pylori causes most peptic ulcers, "eradication of H. pylori" has emerged as a more important indicator of the long-term outcome of treatment. Eradication is a well-validated indicator because long-term studies have shown that eradication reduces the risk of symptomatic ulcers and ulcer complications for several years.

3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in adult patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?

Comment. Another measure of adverse effects is tolerability, measured as the proportion of patients who withdraw from a study due to adverse effects. In general, the PPIs are well tolerated by most patients (mild to moderate gastrointestinal and central nervous system adverse effects are most common).

4. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (2002, Issue 1), MEDLINE (1966-2002), EMBASE (1980-2001), and reference lists of review articles. In electronic searches, we combined terms for gastroesophageal reflux and peptic ulcer with terms for PPIs and relevant research designs (see Appendix A for complete search strategy). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us/index.htm). All citations were imported into an electronic database (EndNote 5.0).

In April 2003, we conducted update searches of the Cochrane Library (2003, Issue 1), MEDLINE (August 2002 through March 2003), and Embase (August 2002 through March 2003) starting from the end-date of the original searches. In electronic searches, we used the same search strategy as was used for the original report. Pharmaceutical manufacturers were invited to submit update dossiers. These submissions were reviewed to identify new citations not previously submitted. All citations were imported into an electronic database (EndNote 6.0).

Study Selection

We included English-language reports of randomized controlled trials of at least 4 weeks' duration, in adult outpatients with symptoms of gastroesophageal reflux, peptic ulcer, or NSAID-induced ulcer. Interventions included a PPI compared with another PPI, another anti-ulcer drug (e.g., H2-RA, prokinetic agent, or antacid), placebo, surgery, or antibiotics alone. For adverse effects, we also included observational studies. Included medications were omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. Outcomes were symptoms, endoscopic healing, eradication rates, functional outcomes, quality of life, and adverse effects, including drug interactions.

To evaluate efficacy we included only controlled clinical trials. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[1-3] Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable, but are also discussed in our report.

Trials that evaluated one PPI against another provided direct evidence of comparative efficacy and adverse event rates. In theory, trials that compare PPIs to H2-RAs or placebos can also provide evidence about efficacy. However, the efficacy of PPIs in different trials can be difficult to interpret because the patients may be different.

To evaluate adverse event rates, we included clinical trials and observational cohort studies. Clinical trials are often not designed to assess adverse events, and may select low-risk patients (in order to minimize dropout rates) or utilize inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to followup, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to followup.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[1, 2] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more

categories were rated poor quality; trials which met all criteria, were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

In addition to discussion of the findings of the studies overall, meta-analyses were conducted where possible. Differences in esophageal or ulcer healing rates are expressed as the "percent risk difference." This is the difference between the proportions healed in two groups of patients at a given time-point (e.g., at 4 weeks, 80% in group A and 75% in group B is a 5% risk difference). In one systematic review,[4] results are reported as relative risks. A relative risk of 2.0 for esophagitis healing with Drug A versus Drug B means that patients taking Drug A are twice as likely to heal as those taking Drug B. As a measure of the variance around these estimates, the 95% confidence interval (CI) is also reported. If the 95% CI includes 0 (or 1 in the case of relative risks), then the difference is not statistically significant. Meta-analysis was done using StatsDirect (CamCode, UK) software. Pooling was done using both fixed and random effects models. Results from the random effects models are presented, unless results from the two methods differed, in which case both would be presented. If significant statistical heterogeneity was found, pooling was not conducted. Random effects logistic meta-regression models were fit to estimate the probability of healing with PPI adjusted for healing rate with H2-RA within the same study. The model stratified by type of PPI (lansoprazole, omeprazole, pantoprazole, and rabeprazole). Posterior distributions were simulated using WinBUGS.[5]

RESULTS

Overview

The original searches and review of reference lists identified 1799 citations: 147 from the Cochrane Library, 815 from MEDLINE, 574 from EMBASE, 231 from reference lists, and 32

from pharmaceutical company submissions. We included 91 randomized controlled trials and six systematic reviews. An additional 29 citations provided information for background, methodology, drug interactions, and adverse effects. We did not examine in detail placebo-controlled trials if studies using an active control were available for a key question (see Appendix C). We excluded reports that were published in abstract form only (see Appendix D).

The update searches conducted through March 2003 identified 265 additional citations, 48 from the Cochrane Central Register of Controlled Trials, 72 from Medline, 90 from Embase, and 55 from two pharmaceutical companies. Of these, 87 were trials, of which 16 met inclusion criteria. We excluded 71 trials for the following reasons: patient population not included (11), no included drug or combined drug therapy where the effect of the PPI could not be distinguished (18), no included outcome measure (3), study reported as abstract only (24), duplicate publication (1), non-English language (12), no control group (1), unable to locate study (1).

Most of the randomized trials had fair internal validity, but their applicability to community practice was difficult to determine. These studies generally excluded patients who had serious medical conditions (the decision of what qualified was left to the investigators). Most of the treatment and control groups received standard doses of anti-ulcer drug, but there were instances of a higher or lower than typical dose used. Of those studies that stated the funding source, all were funded by the pharmaceutical industry, and industry employees often served as co-authors.

1. What is the comparative efficacy of different PPIs in adult patients with symptoms of GERD?

1a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in adult patients with symptoms of GERD?

We identified 12 randomized controlled trials comparing two PPIs for healing of esophagitis and gastroesophageal reflux symptom relief.[6-15, 16, 17] Omeprazole was the comparator in all but two studies.[10, 16] These studies are summarized in Table 2. Four studies compared omeprazole versus lansoprazole,[6, 11, 13, 14] two omeprazole versus rabeprazole,[8, 9] two omeprazole versus esomeprazole,[12, 15] one omeprazole versus pantoprazole,[7] and one lansoprazole versus pantoprazole.[10] one omeprazole versus both lansoprazole and pantoprazole,[17] one esomeprazole versus lansoprazole,[16] and one lansoprazole versus pantoprazole.[10] The scales used to grade esophagitis in these studies are described in Appendix E.

Two [15] studies[15, 16] met all criteria for internal validity, one was rated poor,[11] and the rest were fair. In the poor quality study, eligibility criteria were not specified, so it would be impossible to verify or reproduce the results.

Two studies[6, 16] reported the race of patients enrolled; in one,[6] 85% of participants were white, 9% were black, and 5% were Hispanic; and in the other,[16] 91% were white, 6% were black, less than 1% were Asian, and 2% were classified as "other." Pregnant and lactating women, and women of childbearing potential were excluded from all studies, and the majority of patients enrolled were male. No children (i.e., under age 18) were included in these studies.

Esophagitis Healing

A recent systematic review (Caro)[18] examined esophagitis healing and relapse rates in trials of newer PPIs compared to omeprazole. This study met criteria for a good quality systematic review: it used comprehensive sources and systematic search strategies, explicit and relevant selection criteria, standard appraisal of studies, and drew valid conclusions. The review found that lansoprazole, rabeprazole, and pantoprazole had similar efficacy to omeprazole for healing. No studies of esomeprazole had been done at the time.

Our review of head-to-head trials confirmed this result. All of the PPIs were effective at healing esophagitis. Healing rates at 4 weeks ranged from 61.2% to 91.2%, and at 8 weeks ranged from 71.1% to 94.2%. Figure 1 shows differences in healing rates at 4 and 8 weeks for the eight trials that provided this information. Three studies[8, 12, 16]did not provide number healed/total, and one trial[17]reports only symptom relief, not esophagitis healing. There was no difference between lansoprazole 30mg, omeprazole 20mg, pantoprazole 40mg, and rabeprazole 20mg in healing rates at 4 or 8 weeks. The pooled risk difference for 3 studies that compared lansoprazole 30 mg to omeprazole 20 mg was 1.17 (95% CI –3.02, 5.36) at 4 weeks and 0.76 (95% cI –0.02, 4.29) at 8 weeks. One study[6] found omeprazole 20mg had a higher healing rate than lansoprazole 15mg; however, in the same study, lansoprazole at a higher dose (30mg) was as effective as omeprazole 20mg in healing at 4 and 8 weeks.

Two trials compared esomeprazole 40mg to omeprazole 20mg, and both found a greater healing rate in the esomeprazole group.[12, 15] In the earlier study,[12] raw data are not reported, and results are given as cumulative life table rates only. No other study used this method of analysis, so it is difficult to compare these results with those of studies that reported an intention to treat analysis of simple proportions healed. Using life table analysis may overestimate results by excluding patients who are lost to followup or are withdrawn from the study. A more recent and larger (n= 2425) good quality trial (Richter) from the same group of authors also found esomeprazole 40mg had a significantly higher healing rate at both 4 and 8 weeks than omeprazole 20mg.[15] In the esomeprazole group the healing rate at 4 weeks was 78.6% and at 8 weeks it was 89.9%. This study also reports cumulative life table analysis for healing rates at 4 and 8 weeks. Crude rates and cumulative life table rates in each group were very different. For example, in the esomeprazole group, the cumulative life table rate of healing at 4 weeks was 93.7%, whereas the crude rate was 78.6%.

Although it was well conducted, the applicability of the study is poor for two reasons. First, it compared esomeprazole 40mg to a lower dose (20mg) of omeprazole. One would expect that esomeprazole 40mg, an optical isomer of omeprazole, was equal in potency to omeprazole 40mg, not omeprazole 20mg. There is also no reason to expect that omeprazole 40mg and esomeprazole 40mg differ in toxicity. One study that used omeprazole 40mg found a healing rate of 79.9% at 4 weeks and 90.5% at 8 weeks,[14] comparable to the rates found at esomeprazole 40mg in the Richter study. Rates of symptom relief at 4 weeks were also comparable; neither study reported symptoms at 8 weeks.

Second, the subjects of the study are not described adequately, leaving open the possibility that there was selection bias. The baseline characteristics reported in the article are sex, age, race, H. pylori status, esophagitis grade, duration of GERD, and "heartburn" (none, mild, moderate, severe). It is not clear whether the severity of heartburn was measured before or after the patients had been taken off non-study PPIs and H2-RAs. Selection bias is possible

because patients who were not doing well with omeprazole 20mg to begin with might have been preferentially referred to the study.

Another large, good quality trial compared esomeprazole 40mg to lansoprazole 30mg for acute treatment of erosive esophagitis in 5241 patients at multiple centers in the US.[16] Healing rates were significantly higher in the esomeprazole group at 4 weeks (79.4% vs 75.1%, $p<0.01$) and at 8 weeks (92.6% vs 88.8%, $p=0.0001$) using life-table analyses. As in the Kahrilas study discussed above, crude healing rates are also reported after adjustment for baseline severity, and are lower than the rates using life table analysis at 4 weeks (75.7% vs 71.7%, $p \leq 0.01$) and 8 weeks (87.6% vs 84.2%, $p \leq 0.01$). The unadjusted rates or numbers of patients healed and total included in analysis are not given in the report.

Studies presenting only life-table analyses and adjused rates of healed patients are not included in figure 1 because the numbers of patients healed and unhealed are not reported and cannot be directly compared to the other studies presenting these data.

In summary, our review and a recent good quality systematic review[18] found no differences among omeprazole, lansoprazole, rabeprazole, and pantoprazole in healing rates at 4 and 8 weeks. In two trials esomeprazole 40mg had higher 4-week and 8-week healing rates than omeprazole 20mg, but there are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg. One trial of esomeprazole 40 mg versus lansoprazole 30 mg found better healing rates in the esomeprazole group, At 8 weeks the difference in adjusted crude healing rate was 3.4% corresponding to a number needed to treat of 29 (for every 29 patients treated with esomeprazole one additional patient was healed compared to lansoprazole).

There have been 3 trials that compare esomeprazole to another PPI, but because of concerns over lack of equivalence in doses used (omeprazole), method of reporting and analyzing results, and relatively small differences in healing rates these trials do not provide sufficient evidence that esomeprazole is more efficacious than any other PPI. Clear reporting of numbers of patients healed and unhealed at 4 and 8 weeks in these trials would help to clarify this.

Relief of Symptoms

Eleven head-to-head comparisons of PPIs measured symptom relief as a secondary outcome, [6-15], [16] and patient satisfaction and symptom relief were the primary outcomes in one.[17] Symptoms in these studies were assessed through patient diaries, investigator-elicited reports, or both. Four studies compared symptom relief for lansoprazole versus omeprazole.[6, 11, 13, 14] Although lansoprazole was seen to improve some symptoms at some time points, there was no strong or consistent pattern to suggest that lansoprazole is more effective or provides faster symptom relief than omeprazole. In one study, lansoprazole was more effective for daytime heartburn only, in another it was more effective for nighttime heartburn only, and in two others there was no difference. In one fair quality study,[6] symptoms were elicited by the investigator at each visit, and patients also kept diaries that included episodes of day and night heartburn. There was no difference in symptom relief between lansoprazole 30mg and omeprazole 20mg. Patient diaries showed the lansoprazole group had a lower mean percentage of nights with heartburn over 8 weeks of treatment, but no difference in days with heartburn or days of antacid use. It is difficult to interpret these data because sometimes the data are given as mean percentages and at other times median percentages are given. For example, at week 1, data are given as means, and at week 8 are given as medians. The investigators report that lansoprazole was superior in

symptom relief because after the first day and first week of therapy, patients in the lansoprazole group reported significantly fewer days and nights with heartburn. Results are given as mean percentages. There were no differences in symptoms, as assessed by investigator questioning during visits, which were assessed at 2, 4, and 6 weeks of treatment. Reporting of diary data seems inconsistent and incomplete.

In another fair quality study,[13] day and nighttime heartburn and epigastric pain according to patients' diaries was improved during the first week of treatment in both groups. After 3 days of treatment, there was a significantly greater improvement in daytime heartburn symptoms in the lansoprazole group (p=0.05) as assessed by a change from baseline according to a visual analogue scale ranging from 0 to 100 mm ("no pain" to "worst pain ever"). There was no difference between treatment groups for epigastric pain or nighttime heartburn, and at 7 days the difference in daytime heartburn was no longer significant (p = 0.18). According to clinical assessment, there was more improvement in daytime epigastric pain after 1 and 8 weeks, but no difference at week 4 and no difference between the groups in any other measure of symptoms (day and nighttime heartburn, dysphagia, odynophagia, acid regurgitation). In a good- to fair quality study of lansoprazole 30mg versus omeprazole 40mg,[14] there was no difference between groups in the number of patients reporting no symptoms at 4 weeks. Symptoms at 8 weeks were not measured. A poor quality study[11] also compared symptom relief for lansoprazole 30mg versus omeprazole 20mg. Patients receiving lansoprazole experienced "greater improvement in heartburn" after 4 weeks than patients in the omeprazole group (p=0.03), but details are not given, and no other significant differences in symptoms are reported. After 8 weeks, the difference in heartburn was no longer statistically significant. Two fair quality studies found no difference in symptom relief (heartburn, acid regurgitation, or pain on swallowing) between pantoprazole and lansoprazole,[10] or pantoprazole and omeprazole,[7] at 4 weeks. Symptoms at 8 weeks are not reported.

In the only head-to-head study that measured symptoms and quality of life as a primary outcomes,[17] 461 patients were randomized to either omeprazole Multiple Unit Pellet System (MUPS) 20mg, lansoprazole 30 mg, or pantoprazole 40 mg. Symptom relief was equivalent with omeprazole and pantoprazole at 4 (84% and 84%), and 8 weeks (87 and 89%, respectively). Lansoprazole had lower rates (78% at 4 weeks, 81% at 8 weeks), where both omeprazole and pantoprazole were found statistically significantly superior. These are cumulative rates, patients who resumed having symptoms were continued to be counted as resolved. Patient satisfaction at 4 and 8 weeks was equivalent for all 3 PPIs at 4 and 8 weeks, however. Data at 12 weeks was recorded but not reported. One study measured symptoms at 4 and 8 weeks in a comparison of rabeprazole 20mg versus omeprazole 20mg.[8] On 12 measures of symptom relief and overall well-being, no differences were found between the two groups.

The earlier of two trials of esomeprazole[12] reported shorter time to relief of heartburn and a higher rate of resolution of symptoms at 4 weeks (64.7%) with esomeprazole 40mg than omeprazole 20mg (57.2%) or esomeprazole 20mg (61.0%). The number of days until the first heartburn-free day, number of days until sustained resolution of heartburn (7 consecutive days without heartburn), and number of heartburn-free days and nights were all improved with esomeprazole 40mg compared with the other preparations. This study reports that by day 1, 29.9% of patients in the esomeprazole group already had sustained resolution of symptoms, so the validity of this measure is not clear. In the second, larger trial, resolution of heartburn by 4 weeks was 68.3% for esomeprazole 40mg versus 58.1% for omeprazole 20mg ($p < 0.001$).[15] Neither study reported symptom outcomes at 8 weeks.

A good-quality trial[16] of esomeprazole 40 mg versus lansoprazole 30 mg reports more patients with sustained resolution of heartburn in the esomeprazole group, as judged by investigator assessment of patient diaries, at 4 weeks (62.9% vs 60.2%, $p \leq 0.05$). This difference in risk is 2.7%, corresponding to a number needed to treat of 37. Complete resolution of heartburn was defined as 7 consecutive days without heartburn. Sustained resolution of heartburn occurred faster with esomeprazole (7 days vs 8 days, $p \leq 0.01$). There was also faster resolution of nocturnal heartburn and a greater percentage of heartburn-free nights in the esomeprazole group, but no difference in percentage of heartburn-free days, or in the time to first resolution of heartburn and nocturnal heartburn. Symptoms at 8 weeks were not reported.

Prevention of Relapse

Three randomized controlled trials compared one PPI to another for long-term (6 months or more) maintenance therapy for esophagitis relapse prevention (Table 3).[4, 19, 20] Two of these found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks of treatment,[4] or rabeprazole versus omeprazole after 13, 26, and 52 weeks,[19]

A recent head-to-head trial[20] compared relapse rates at 6 months in patients randomized to esomeprazole 20 mg or lansoprazole 15 mg. Only those patients who were healed and symptom-free after using esomeprazole 40 mg for 4 to 8 weeks were enrolled in the maintenance phase of the study. According to life-table analysis, a higher proportion of patients in the esomeprazole group remained healed (83% vs 74%) over 6 months. The authors also present data by baseline severity. More patients in the esomeprazole group remained healed across all grades of disease severity, whereas the efficacy of lansoprazole decreased with increasing severity of disease. No crude rates or numbers of patients remaining healed were presented. Crude rates provide a more conservative estimate of effectiveness due to the manner in which drop-outs are handled in life-table analyses. Because all patients enrolled had responded to esomeprazole for initial healing of esophagitis, the study may be biased towards esomeprazole.

A shorter-term trial of 36 patients with severe (Savary-Miller Grade 4) esophagitis compared omeprazole, lansoprazole, and pantoprazole for the prevention of relapse at 4 weeks.[21] Before randomization, all of the patients were treated with omeprazole. Six patients did not heal after 6 to 8 weeks of omeprazole; the remainder (83%) were randomized to omeprazole, lansoprazole, or pantoprazole. After 4 weeks, patients taking omeprazole had a lower rate of endoscopic relapse (10%) than those randomized to either lansoprazole (80%) or pantoprazole (70%). The relapse rates in the lansoprazole and pantoprazole groups are very high compared with other studies and, as in the esomeprazole versus lansoprazole study discussed above, had a selection bias in that all subjects had responded well to one of the study drugs before enrollment in the maintenance phase.

1b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?

Comparisons of PPIs across studies is difficult because patient populations and baseline healing rates are dissimilar.

Esophagitis Healing

In the systematic review mentioned above,[18] four PPIs were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included.[18]

Twenty-one randomized controlled trials compared a PPI with an H2-RA for GERD. Figure 2 shows the rates of esophagitis healing at 8 weeks in 20 of these (full text of one study[22] was unavailable. These trials compared an H2-RA to omeprazole (10 studies[23-33] lansoprazole (five studies),[34-38] pantoprazole (four studies),[39-43]and rabeprazole (1 study).[44] We did not create evidence tables of these studies or rate their quality, because after graphing their results we found no indication that the PPIs differed. If an obvious difference in healing rates were seen in an individual study or studies, investigation of study quality would have been undertaken. In our meta-analysis, PPIs were more effective at healing than H2-RAs, but there were no differences in healing rates among the PPIs for any comparison. Healing rates ranged from 71.2% to 85.6%.

Relief of Symptoms

In the Caro systematic review,[18] the pooled relative risk of studies that reported heartburn resolution at 4 weeks was 1.02 (95% CI, 0.94-1.11) for newer PPIs (pantoprazole, rabeprazole, lansoprazole) compared with omeprazole. For all 4 PPIs versus ranitidine, the pooled relative risk was 1.53 (95% CI, 1.37-1.72).

Prevention of Relapse

The Caro systematic review identified 15 studies of relapse prevention.[18] Only three of them compared one PPI to another, and all three were abstracts rather than full-text reports. Seven compared a PPI to placebo, and five compared a PPI to ranitidine. The review found similar remission rates for lansoprazole, rabeprazole, and omeprazole over 12 months of treatment. Relapse rates at 6 months were 6% to 29% with lansoprazole, 9% with rabeprazole, and 7% to 42% with omeprazole.

2. What is the comparative efficacy of different PPIs in adult patients with peptic ulcer and NSAID-induced ulcer?

2a. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?

Nine randomized controlled trials compared one PPI to another.[8, 45-52] The details of these studies are summarized in Table 4. Six of these trials compared lansoprazole 30mg to omeprazole 20mg.[45-49, 52] One study each compared pantoprazole 40mg and rabeprazole 20mg to omeprazole 20mg[8, 50] and one study comparing esomeprazole 40mg to omeprazole 40mg.[51] All of these dose comparisons are fair based on equipotency.

The studies were fair quality. These studies were generally similar with respect to design, demographics and other population characteristics, with the following exceptions. One

study was unusual in that as a part of a H. pylori eradication regimen, patients with active duodenal ulcer were given esomeprazole plus antibiotics for only 1 week, while omeprazole patients received antibiotics plus omeprazole for 1 week, then continued omeprazole for another 3 weeks.[53]

As shown in Figure 3, there was no difference between omeprazole 20mg, lansoprazole 30mg, and rabeprazole 20mg in the percentage of patients healed by 4 weeks. Results from a large multicenter trial of esomeprazole 40mg versus omeprazole 40mg also showed no difference in healing rates.[51] The pooled risk difference for lansoprazole 30mg versus omeprazole 20mg once a day was -0.2 (95% CI, -3.0-2.6). The risk differences found between esomeprazole 40mg, pantoprazole 40mg and rabeprazole 20mg and omeprazole were approximately –0.97%, 6% and 5%, respectively, however these are based on single studies and were not statistically significant. The results for healing at 2 weeks were similar.

Symptoms (pain, nausea, vomiting, antacid use, or overall well-being) were assessed by investigators at visits and through patient diaries in seven studies. Only one found a significant difference between PPIs.[8] This study found that daytime pain was 'improved' in 92% on rabeprazole and 83% on omeprazole at 4 weeks (p=0.038), however no difference was found in nighttime pain or in the number of patients who were pain-free. Antacid use, GI symptoms, and overall well-being were not different in any of the studies.

Only one head-to-head study addressed maintenance, comparing lansoprazole 15mg, lansoprazole 30mg and omeprazole 20mg for up to 12 months (see Table 5).[48] At 6 months post-healing, recurrence rates were 4.5%, 0%, and 6.3%, respectively. At 12 months the recurrence rates were 3.3%, 0%, and 3.5%, respectively. These differences were not statistically significant. Three other studies listed in Table 5 compared lansoprazole to placebo[54, 55] or ranitidine.[56] Relapse rates at 12 months in the lansoprazole 15mg groups ranged from 23 to 30%, in the single lansoprazole 30mg group the rate was 15%, compared to placebo rates of 39 to 100%. One study reported relapse rates with no maintenance treatment following healing with omeprazole, ranitidine or placebo. Relapse rates were not significantly different between the groups.

2b. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?

Twenty-five randomized controlled trials compared a PPI with an H2-RA. Of these, 22 papers were reviewed.[57-77];Archambault, 1996 #2216} Since these studies can only be used to make indirect comparisons of the effectiveness of the various PPIs, a limited analysis is presented. Individual study quality assessments for these studies will not be presented. If an obvious difference in healing rate were seen in an individual study or studies, investigation of study quality would have been undertaken.

The most common H2-RA used as a comparator was ranitidine 300mg per day, with ten studies comparing omeprazole 20mg, four studies comparing pantoprazole 40mg, two studies comparing lansoprazole (doses varying from 15 to 60mg per day), and one study comparing rabeprazole 20mg. Two compared omeprazole 20mg to cimetidine (doses varying from 800mg to 1200mg per day), two compared omeprazole 20mg with famotidine 40mg, and 1 compared omeprazole with nizatidine 300mg. There are no studies comparing esomeprazole to an H2-RA.

Figure 4 shows the rates of duodenal ulcer healing at 4 weeks in 21 studies of a PPI versus an H2-RA PPIs were more effective at healing than H2-RAs, but there were no significant

differences in healing rates among the PPIs. Duodenal ulcer healing rate at 4 weeks with omeprazole and lansoprazole was dependent on H2-RAs healing. That is, as the healing rate in the H2-RA group increased, PPI healing rate increased. One comparison showed pantoprazole to have a significantly higher healing rate than rabeprazole (risk difference 11.3%), but this comparison is based on only one study, and the confidence interval is large (95% CI, 2.4%-23.2%).

Another study[78] examined the added benefit of continuing omeprazole 20 mg for 3 additional weeks after 1 week of eradication therapy with omeprazole 20mg combined with amoxicillin 1000 mg and clarithromycin 500 mg. At 4 weeks, there was no difference in healing rates in patients assigned to omeprazole (89%) versus placebo (87%).An additional four trials were found in updating the original review[22, 79-81] These studies were consistent with the studies reported above and are not added to figure 4. One of these studies reported symptom relief only.[81]

2c. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?

Only one study compared one PPI to another in the treatment of gastric ulcer.[82] This fair quality study of 227 patients compared rabeprazole 20mg to omeprazole 20mg and is summarized in Table 6, with the other gastric ulcer studies. Healing was assessed at 3 and 6 weeks, while most other studies of gastric ulcer healing use 4 and 8 weeks. The percent risk difference in the rate of healing at 3 weeks is -3% (95% CI, –16, 9.7), and reported as the same in both groups at 6 weeks.

Symptoms were assessed by investigators at visits and through patient diaries. Twelve different comparisons of symptom resolution or improvement were made. No significant differences were found in the reporting of pain resolution or improvement (frequency, severity, night or daytime) at 3 or 6 weeks for nine of these comparisons. Rabeprazole was statistically superior in three comparisons: improvement of severity of pain at 3 weeks and improvement in the frequency of daytime pain and resolution of nighttime pain at 6 weeks. No difference in changes in overall well-being or reduction in antacid use were found.

2d. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?

Fourteen studies compared a PPI to an H2-RA for treatment of gastric ulcer (Table 6).[49, 57, 83-94] There were two studies of maintenance therapy and one followup study of relapse rates in patients healed in one of the above studies.[55, 95, 96] One of the maintenance studies included patients with either gastric or duodenal ulcer, all of which were resistant to H2-RA therapy.[95] No study compared esomeprazole or rabeprazole to a H2-RA. Five trials compared omeprazole to ranitidine; three compared lansoprazole to ranitidine; one compared pantoprazole to ranitidine; two, lansoprazole to famotidine; three, omeprazole to cimetidine, and one, lansoprazole to cimetidine.

The total followup times varied, but healing rates at 4 weeks were available from all studies . Differences in the percentages of patients healed with different PPIs at 4 weeks are

plotted in Figure 5 The pooled risk differences range from 1.09 to 62.5%, with the smallest studies showing larger effects. The confidence intervals for PPIs compared to H2-RAs all overlap.

Symptoms were assessed by investigators at visits and through patient diaries in 13 studies. One did not report symptoms.[85] Pain was the most commonly assessed symptom. The scales used were not consistent across the studies (0 to 3 in some, 0 to 4 in others), or were not described. Most found the PPI relieved symptoms somewhat faster, with no difference later on. However, only three studies found statistically significant differences, and then only in some of the many measures assessed.

One study[97] reported maintenance therapy of lansoprazole 15 or 30mg compared to placebo. Lansoprazole was effective for preventing endoscopic recurrence and eliminating symptoms and reducing antacid use. Omeprazole 20 mg every day was more effective than ranitidine in preventing relapse in patients with refractory ulcer (not healed after 8 weeks of H2-RA treatment) in one 6-month open study.[95] Only 12 patients of 102 enrolled were assigned to ranitidine in this study, and patients with both gastric and duodenal ulcer were included. A 6-month followup study without treatment[96] of patients who had healed after 6 weeks of treatment with omeprazole or cimetidine[84] found no significant difference in relapse rates. All of these studies had high or differential dropout rates.

2e. In head-to-head comparisons, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with NSAID-induced ulcer?

No study compared one PPI to another.

2f. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with NSAID-induced ulcer?

Three studies assessed PPIs compared to another drug in healing ulcers induced by NSAIDs.[98-100] The details of these studies are summarized in Table 7.

Figure 6 shows the risk differences for healing of NSAID-induced gastric ulcers at 8 weeks. All confidence intervals overlap, regardless of comparison.

Symptoms (GI pain, dyspepsia, heartburn, reflux, and antacid use) were assessed at visits (none, mild, moderate, severe) and by patient diary in all studies. Results for symptoms did not include all those measured. In those symptom categories reported, improvement was not different between omeprazole 20mg and 40mg or between lansoprazole 15mg and 30mg, but was superior to the comparator drug.

One study[99] assessed quality of life using the Gastrointestinal Symptom Rating Scale and the Nottingham Health Profile. Based on the Gastrointestinal Symptom Rating Scale, omeprazole was better than misoprostol in the changes in scores for the total scale, as well as scores for reflux and diarrhea. Although the improvement in score was greater with 20mg omeprazole than 40mg, these were not statistically significant. Only the sleep score of the Nottingham Health Profile was reported, which also showed omeprazole 20mg to be superior to misoprostol, but the change in score for omeprazole 40mg was not reported.

2g. In head-to-head comparisons, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

There are no head-to-head comparison studies.

2h. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in preventing NSAID-induced ulcer?

One recent, good quality systematic review addressed this question.[101] The search for literature covered 1966 to 2000 (MEDLINE search from 1966 to January 2000, Current Contents for 6 months prior to January 2000, EMBASE to February 1999, and a search of the Cochrane Controlled Trials Register from 1973 to 1999). This review found five randomized trials, which assessed omeprazole 20 to 40mg in prevention of NSAID-induced gastroduodenal toxicity. None of the studies were designed to evaluate the effectiveness of PPIs in preventing serious ulcer complications (hemorrhage, perforation or death). The review showed that omeprazole is superior to the H2-RAs but provided no data on any other PPI.

Four trials published more recently[102-105]are presented in Table 8, along with two of the treatment studies that included a prevention phase.[99, 100] None of these studies was a head-to-head comparison and there were important differences in treatment regimens and followup, making comparisons across studies impossible. One study[102] included only patients who were H. pylori negative and randomized to placebo, misoprostol 800mcg, lansoprazole 15mg or 30mg with followup at 1,2 and 3 months, another[103] randomized patients to pantoprazole 40mg or placebo for 3 months. The third study[104]included patients who were H.pylori positive and had ulcer complications after using low-dose aspirin continuously for more than one month. After ulcers were healed and H. pylori eradicated, patients were randomized to lansoprazole 30 mg or placebo, in addition to 100 mg of aspirin daily. In the last study,[105] H.pylori positive patients with no past or current ulcer were assigned to one of 4 treatment groups: omeprazole 20 mg plus clarithromycin 500 mg and amoxicillin 1 gram for one week, followed by placebo or omeprazole 20 mg daily for 4 weeks; omeprazole 20 mg once daily for five weeks; or placebo for 5 weeks.

In the study of H. pylori negative patients,[102] lansoprazole was inferior to misoprostol in preventing gastric ulcers. At 3 months, the gastric ulcer rate (failure rate) was 7% for misoprostol, 20% for lansoprazole 15mg, and 18% for lansoprazole 30mg, with no significant difference between lansoprazole doses. However, when adverse effects were included as failures, the failure rate for all 3 treatment groups was 31%.

In the study of pantoprazole versus placebo,[103] a life-table analysis is presented, rather than simple proportions of patients without ulcer, making comparison to other PPI versus placebo studies unclear. At 4 weeks, the risk difference is 17% fewer ulcers in the pantoprazole group, and 27% at 12 weeks. These numbers include those who dropped out due to adverse effects as treatment failures.

In the study of H.pylori positive patients with ulcer complications,[104] the primary endpoint was prevention of ulcer complications and the secondary endpoint was recurrence. The rate of recurrence of ulcer complications at a median followup of 12 months was 1.6% in the lansoprazole group, compared with 14.8% in the placebo group. Two patients in the placebo group were also taking NSAIDS.

In patients with H.pylori but no history of ulcer, all 3 active treatment regimens were better than placebo in reducing the occurrence of ulcer and dyspeptic symptoms requiring therapy, and there were no significant differences between the treatment groups.

Symptom assessment and reporting varied among these studies. The pantoprazole versus placebo study did not describe methods or scales used to assess symptoms, but reported "GI symptoms."[103] GI symptoms were not the same at baseline in the two groups; 43% in the pantoprazole versus 18% in placebo group complained of GI symptoms. At 4 and 12 weeks the pantoprazole group improved (17% and 20%, respectively), while the placebo group remained stable (20% and 19%, respectively). In the lansoprazole versus misoprostol study, symptoms (day and nighttime abdominal pain and antacid use) were assessed by patient diary and were found to be significantly better in the lansoprazole groups versus misoprostol, but comparisons between the two lansoprazole doses were not made.[102]

2i. In head-to-head comparisons, what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?

One recent, fair quality systematic review addressed this question.[106] The search for literature covered 1986 to1998 (MEDLINE search from 1986 to 1997, and hand searches from 1986 to January 1998). This meta-analysis included 666 studies overall. Although the number of studies evaluating a PPI is unclear, there were nine different regimens that included a PPI. The PPIs included in these studies were omeprazole, lansoprazole, and pantoprazole. Using a meta-regression analysis, no difference in cure rate was found between the three PPIs in any of the antibiotic combinations studied. Another recent fair quality systematic review focused on lansoprazole in eradication of H. pylori.[107] This review found no difference between lansoprazole and omeprazole in eradication rate.

Since this review, 16 studies were published that directly compared one PPI to another in combination with the same antibiotic(s).[51-53, 108-120]They made the following comparisons:

- rabeprazole 20mg versus omeprazole 40mg, plus amoxicillin (one study)[108]
- lansoprazole 60mg versus omeprazole 40mg, plus amoxicillin and metronidazole(one study)[110]
- omeprazole 40mg versus pantoprazole 40mg, plus clarithromycin and metronidazole (one study)[117]
- omeprazole 20mg versus lansoprazole 30mg, plus clarithromycin and tinidazole (one study) [52]
- various doses of lansoprazole, rabeprazole, pantoprazole and esomeprazole versus omeprazole, plus clarithromycin and amoxicillin (nine studies)[51, 53, 109, 111-116]
- omeprazole 20 mg, lansoprazole 30 mg, or rabeprazole 10mg (all twice daily) each combined with amoxicillin and clarithromycin (one study),[118]
- rabeprazole 20mg or lansoprazole 30mg twice daily, each combined with amoxicillin and clarithromycin (one study),[119]
- lansoprazole 30 mg or omeprazole 20 mg twice daily combined with amoxicillin alone, versus lansoprazole 30 mg twice daily combined with amoxicillin and clarithromycin (one study).[120]

None of these studies was conducted in the US. Seven were conducted in Japan, two in Italy, one in England, one in Germany, one in Sweden, two in multiple European countries, one in Canada, and one in Colombia.

These studies were fair quality, with the exception of one fair to poor quality study that was not blinded.[108] This is a heterogeneous group of studies. Some of the PPI comparisons did not use what would be considered equivalent doses (e.g., rabeprazole 20mg versus omeprazole 40mg or omeprazole 40mg versus pantoprazole 40mg) and one used a dose of omeprazole that is not standard in the US (60mg).[116] In addition, the doses of clarithromycin, amoxicillin and metronidazole also vary. Some of the studies were assessing short durations of treatment, while others were evaluating the use of lower doses of PPIs in Asian patients (see Key Question 3). The methods of assessing H. pylori eradication also varied among the studies, as did other treatments during the study period. Hence, direct comparison across all studies is not possible.

Nine studies included patients with documented ulcer.[51-53, 108, 110, 111, 115, 118, 119]Five studies included patients with ulcers or non-ulcer dyspepsia[109, 112-114, 117] The proportion of non-ulcer patients ranged from 12%[112] to 71%.[114] One study conducted in a low-income population in Colombia included patients with "gastritis" and did not check for ulcer,[116] and one included both patients with previous or present recurrent ulcer.[120]

As would be expected based on these differences, eradication rates varied in these studies, from a low of 62.5% (rabeprazole 20mg)[108] to a high of 100% (pantoprazole 40mg).[117] One study found a significantly lower eradication rate for pantoprazole (40mg) than for omeprazole 40mg or high-dose pantoprazole (80mg), and another found a lower rate for rabeprazole (20 mg or 40 mg) than lansoprazole 30 mg.[119] No other study found a significant difference regardless of dose or specific PPI.

2j. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?

Three fair quality systematic reviews assessed PPIs compared to H2-RA-based eradication regimens.[106, 121, 122] All three found similar eradication rates for the PPIs compared to H2-RAs.

3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in adult patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?

Adverse Events

There are no head-to-head long-term comparison studies designed to assess adverse events between PPIs. In three long-term maintenance studies of patients with GERD, there was no difference in the number of adverse events reported or number of withdrawals due to adverse events in the different PPI treatment groups. In one study of GERD patients,[4] 9 of 248 (3.6%) patients withdrew for adverse events over 48 weeks of treatment, 4% in the lansoprazole group and 3.3% in the omeprazole group. In another study, comparing rabeprazole 10 or 20mg to

omeprazole 20mg,[19]13 of 243 (5.3%) patients withdrew because of adverse events; the numbers in each group did not differ significantly. Seven patients each in the rabeprazole 10mg and 20mg groups, and 8 patients in the omeprazole 20mg group reported serious adverse events. In the third long-term maintenance study,[123]29 of 617 (4.7%) patients in the esomeprazole 20 mg group and 32/614 (5.2%) of those in the lansoprazole 15 mg group withdrew due to adverse effects. There are no head-to-head maintenance studies of ulcer, but three 12-month studies of duodenal ulcer maintenance compared a PPI to placebo or other anti-ulcer medications. In two of the studies, the withdrawal rates for placebo were higher than any of the drug arms. In one study, the withdrawal rates due to adverse events were high, 17% for lansoprazole 15mg, 5.3% for lansoprazole 30mg and 21.5% for placebo over a 12-month period.[55]

Several reports of long-term (1 year or more) followup of individual PPIs (omeprazole, lansoprazole, and pantoprazole) have been published.[124-137] The potential adverse effects studied include hypergastrinemia related enterochromaffin-like cell (ECL) hyperplasia and ECL carcinoids, atrophic gastritis and intestinal metaplasia, overgrowth of gastric bacteria and N-nitrosamine formation, enteric infections, potential malabsorption syndromes, and diarrhea. Of these, the risk of enteric infections may be increased with sustained acid suppression. This is a rare event, however. The other concerns have not been proven in these long term, non-comparative studies. While ECL hyperplasia occurs, no increased risk of ECL carcinoids has been found. Likewise, atrophic gastritis is increased with long term PPI therapy, but progression to intestinal metaplasia and gastric cancer has not been shown. Gastric bacterial overgrowth does occur, but a related higher rate of gastric adenocarcinoma has not been found. Long-term studies assessing the risk of esophageal cancer were not found. A nested case-control study of 10,008 lansoprazole users followed for 4 years found a trend for diarrhea to be dose related, reported in 5%, 3.7%, and 2.5% of patients using 60 mg or more, 30 mg, and 15 mg or less, respectively (p=0.08). In 42.1% of patients reporting diarrhea the lansoprazole dosage was reduced or discontinued due to this event. Cases had a higher current use of oral antibiotics than controls with no diarrhea (adjusted OR 2.7, 95% CI 1.0-6.9). There are no long-term studies of esomeprazole or rabeprazole.

Reports of adverse effects in head-to-head comparisons of PPIs for short-term treatment of GERD and ulcer are shown in Table 9. The proportion of patients withdrawing due to adverse events in these studies was very low, with most studies reporting 1% to 3%. No study found significant differences among treatment groups in the rate of withdrawals for adverse effects. The exception was one study of rabeprazole 10mg or 20mg versus omeprazole 20mg that reported 5% to 7% withdrawals for adverse events.[9] The rate of attrition overall was somewhat high in this study (17%-24%).Reports of serious adverse events were low, and generally balanced among the drugs. Many of these incidences could be associated with pre-existing diseases.

Serum gastrin levels were monitored in several studies, and found to be significantly elevated compared to baseline although the magnitude of increase was small and generally not considered clinically significant. A dose-related difference was found in some studies, but no differences between drugs. Likewise, when studied, the effect of the individual PPIs on H. pylori-related gastritis was similar, worsening gastritis in the corpus, and improving gastritis in the antrum.[138]

Also in Table 9 is a head-to-head study designed to determine patient preferences about switching from one PPI to another.[139]The study included patients who had been taking a PPI for any indication for at least 56 days before the start of the study. All patients took omeprazole 20

mg and rabeprazole 20 mg daily for 4 weeks in a crossover design, with the order of medication randomized. A double-dummy presentation was used to blind patients to treatment assignment. At the end of each 4-week treatment phase patients were asked to name any unwanted or welcome side effects from the medication. The two PPIs maintained similar relief of symptoms, and the tolerability was similar.

Drug Interactions

There are no head-to-head comparative studies of drug interactions with PPIs in patients with acid-related diseases. Drug interaction studies in healthy adults have been done with individual PPIs, and are summarized in Table 10. All of the PPIs reduce the absorption of drugs that require an acidic gastric pH for maximal absorption, such as ketoconazole. With all of the PPIs, the dose of these drugs may need to be increased, or the drug combination avoided (e.g., delaviridine and PPIs). All of the PPIs are metabolized by the CYP2C19 and CYP2A4 enzyme systems, and have some potential for interacting with other drugs that are also metabolized through this pathway. As can be seen in the table, omeprazole interacts with several drugs, but only four require any action (carbamazepine, phenytoin, diazepam and trovafloxacin). The recommended action is to monitor the patient for signs of adverse effects due to increased levels of these drugs. The newer PPIs have fewer studies of drug interactions, but in the studies that have been done, no clinically significant drug interactions have been found. The one possible exception to this is the decreased clearance of theophylline with lansoprazole. Since these studies have been done in healthy people, the external validity of the judgment of no clinical significance is unknown.

Table 10: Clinically Significant Drug Interactions

	Omeprazole	Esomeprazole	Rabebrazole	Lansoprazole	Pantoprazole
Drugs with pH dependent absorption (e.g. ketoconazole, iron, digoxin, delaviradine, indinivir, enteric coated salicylates)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)
Carbamazepine	Monitor (1)				No significant interaction (3)
Clarithromycin	No specific action required (1)	No significant interaction (2)			No significant interaction (3)
Clorazepate	No specific action required (1)				
Cyclosporine	No specific action required (1)				
Diazepam	Monitor (1)	No significant interaction (2)	No significant interaction (4)	No significant interaction (4)	No significant interaction (3)
Disulfiram	No specific action required (1)				
Methotrexate	Monitor (1)				
Nifedipine	No specific action required (1)				No significant interaction (3)
Phenytoin	Monitor (1)	No significant interaction (2)	No significant interaction (4)		No significant interaction (4)
Tacrolimus	No specific action required (1)				
Tolbutamide	No specific action required (1)				
Trovafloxacin	Monitor (1)				
Warfarin	No specific action required (1)	No significant interaction (2)	No significant interaction (4)	No significant interaction (4)	No significant interaction (3)
Quinidine		No significant interaction (2)			
Amoxicillin		No significant interaction (2)			No significant interaction (3)
Oral contraceptives		No significant interaction (2)		No significant interaction (4)	No significant interaction (3)
Midazolam					No significant interaction (3)
Metoprolol					No significant interaction (3)
Diclofenac					No significant interaction (3)
Theophylline			No significant interaction (4)	Decreased Clearance (4)	No significant interaction (3)
Glyburide					No significant interaction (3)
Antipyrene					No significant interaction (3)
Metronidazole					No significant interaction (3)
Prednisone				No significant interaction (4)	

(A) These interactions could occur with any of the PPIs due to acid reduction

Refs: (1)Drug Interactions, Facts and Comparisons; (2) esomeprazole manufacturer submission; (3) pantoprazole manufacturer submission; (4) Review of PPI drug interactions by Humphries (employee of manufacturer of rabeprazole.

4. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

In head-to-head comparisons, no sub-groups based on demographics, other medications, or co-morbidities were studied. In included head-to-head studies, the populations included were middle aged, with mean ages ranging from a low of 43,[54] to a high of 70.[104] From 38% to 89% of the patients enrolled were male. The ethnicity of participants was only stated in four trials,[6, 16, 20, 54]. In these studies (3 conducted in the US, one[20] in Europe and South Africa), the patients enrolled ranged from 76% to 98% white. Of the remaining studies, 25 were conducted in European countries (including five in Italy), five in Japan, two in the US, and two in Taiwan. The effect of co-morbidities, or other medications were not studied in these trials.

An age-based analysis of healing or prevention was not possible in most trials, due to the small numbers of older patients. However, two trials did assess the impact of age, gender and race on the incidence of adverse effects.[12, 82] There were no differences between PPIs based on these characteristics.

In trials comparing a PPI to another drug, the same general statements can be made, but few findings deserve comment. Studies of healing NSAID-induced ulcer, and prevention of NSAID-induced ulcer included more women than men with the proportion of women ranging from 62 to 67%, and 64 to 83%, respectively. This is most likely due to the greater prevalence of women in the diseases requiring long-term NSAID treatment. However, no gender-based analyses were presented.

The PPIs are all metabolized, largely by the CYP2C19 and CYP3A4 liver enzymes. This enzyme is estimated to be deficient in 3% of white and African Americans, and 17-25% of Asians. This results in a significantly longer half-life, although clinically significant accumulation of these drugs has not been shown. While dose adjustments are not required, and adverse effect profiles of the drugs do not differ, there is some evidence that lower doses may be equally effective in these populations,[113, 140] and that rapid metabolizers may have a higher failure rate in eradicating H. pylori.[108, 109] Results of subgroup analysis found no effect by race in one study of esomeprazole and lansoprazole in healing erosive esophagitis[16].
Older patients also metabolize PPIs more slowly, resulting in significantly higher drug levels and half-lives. However, accumulation has not been shown, and dose adjustments are not recommended. One re-analysis of data from two trials of omeprazole versus either ranitidine or cimetidine for reflux esophagitis examined differences in effects in those age 65 or older compared to under age 65.[141] In this analysis, there were no differences in healing rate or in symptom resolution at 4 and 8 weeks, with slightly higher proportion of older patients both healed and symptom-free. Withdrawals due to adverse events were higher in the older group, 7.6% versus 2.5%. This was not a comparative trial, and similar data are not available for other PPIs.

SUMMARY AND DISCUSSION

Results for the key questions are summarized in Table 11. In general, there is very little evidence that there are any important differences in the effectiveness or safety of the five PPIs in the general population, or in relevant subgroups. The majority of the studies had fair internal validity, but poor external validity with highly selected patient populations.

GERD

There is good evidence that there is no comparative difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis or relief of GERD symptoms. Twelve head-to-head trials, 21 trials of these PPIs versus an H2-RA, and a good quality systematic review have found these four PPIs to be equally effective. The evidence for the effectiveness of esomeprazole is fair. Two trials found esomeprazole 40mg to be more effective than omeprazole 20mg. The justification for using esomeprazole 40mg rather than 20mg in these studies is that these are the FDA approved doses, not necessarily equivalent doses. There are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg. Another study found esomeprazole 40mg had higher healing rates than lansoprazole 30mg when results were presented by life-table analysis or adjusted for severity at baseline. While the differences reported are statistically significant, they appear to be relatively small. The absolute risk difference in healing at 8 weeks was 3.8% by life-table analysis and 3.2% by adjusted crude rate analysis (NNT 26 and 29). The absolute risk difference in proportion with resolution of heartburn symptoms at 4 weeks was 2.7% (NNT 37). Because the esomeprazole studies use different methods of reporting and analyzing data, it is difficult to compare the results to results from other studies of PPIs for esophagitis.

Duodenal Ulcer

The data regarding comparative effectiveness of various PPIs for treating duodenal ulcer is good, with nine head-to-head trials. Omeprazole 20mg daily is typically the comparator drug. The evidence is good for omeprazole and lansoprazole having similar effectiveness in both endoscopic healing and symptom relief. The pooled risk difference for five trials of lansoprazole 30mg versus omeprazole 20mg once daily is -0.2 (95% CI, -3.0-2.6). This translates to a number needed to treat of -5, meaning that for every one patient receiving omeprazole, five additional patients need to receive lansoprazole to achieve healing at 4 weeks in one patient. The evidence for pantoprazole, rabeprazole and esomeprazole is less strong, because there are only single studies for each drug compared to another PPI (all compared to omeprazole). No study found significant differences in healing rate. Data from studies comparing PPIs to H2-RAs also indicate that there are no significant differences between the four PPIs studied (there are no studies of esomeprazole).

Symptom relief is an important measure in ulcer diseases, and does not always correspond to endoscopic healing. Method for assessment of symptom relief was not consistent across the studies, and reporting of findings was often limited to early time periods and just a few outcome measures (of many measured). Few studies found a difference in any of the many measures of symptom relief, and the lack of reported data at later time-points may indicate that symptom relief was equivalent.

Gastric Ulcer

There is little head-to-head comparative data of PPIs for the treatment of gastric ulcer, with only one study of rabeprazole versus omeprazole. No significant differences in healing rates were found. Data from studies of omeprazole, lansoprazole and pantoprazole compared to H2-RAs indicate no significant difference in the rate of healing at 4 weeks.

Symptom relief was better in 3 of 12 measures for rabeprazole compared to omeprazole at 3 weeks or two measures and 6 weeks for a third measure (the measures significantly different at 3 weeks were not different at 6 weeks). Symptom relief was difficult to compare for the other drugs, with no head-to-head studies. No important difference was clear from the PPI versus H2-RA studies.

NSAID-induced Ulcer

There are no head-to-head trials, so the strength of the evidence for comparing PPIs is poor. Only three trials compared a PPI to another drug, two with omeprazole and one with lansoprazole. No important differences between PPIs could be discerned from these studies, with the confidence intervals for healing rates overlapping. However, the treatment success rates for all treatments varied widely among the trials, so confidence in this finding is low.

Prevention of NSAID-induced Ulcer

There are no head-to-head trials. A good quality systematic review and six subsequently published trials compared PPIs to placebo or other drugs. Only one trial included outcome measures for serious ulcer complications, and for some of the endoscopic ulcer findings, patients were asymptomatic. Based on development of new ulcers or serious erosions and on symptoms, there did not appear to be differences in the PPIs studied (omeprazole, lansoprazole and pantoprazole). However, because of the differences in patient populations, comparison groups, and outcome measure definitions, confidence in this finding is low.

Helicobacter Pylori Eradication

The data regarding comparative effectiveness of various PPIs for eradicating H. pylori is fair, with one systematic review, and 16 recent head-to-head trials. The significant heterogeneity among studies based on design, participants, and method of measuring outcomes lessen the strength of the evidence. These studies generally did not find a difference in eradication rate between the PPIs, with the exception of lower dose pantoprazole when compared to high dose pantoprazole or high dose omeprazole, and rabeprazole when compared to lansoprazole in one study. Symptom resolution was not assessed in these studies.

Complications

The comparative evidence on long-term adverse effects is limited. Two long-term (48-52 weeks) maintenance studies found no difference between omeprazole and lansoprazole in adverse events or withdrawals due to adverse events, and a 6-month study of esomeprazole 20 mg versus lansoprazole 15 mg found no differences in adverse event rates. There are no long-term head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects. In long term followup studies of individual drugs, no important differences in long-term findings were apparent, but comparisons across these studies is not clear. Short-term head-to-head comparative studies indicate that the incidence of all and serious adverse events, and the drop out rate due to adverse events for all the PPIs is low. No consistent differences between the PPIs were seen in these trials.

All PPIs share drug interactions based on elevated gastric pH altering absorption of a small number of drugs. Omeprazole is known to have drug interactions with a small number of drugs metabolized by the CYP2C19 and CYP2A4 enzyme systems. The action required is monitoring to see if dose adjustment of the other drug(s) is necessary. Lansoprazole may possibly interact with theophylline. Pantoprazole, rabeprazole, and esomeprazole have no documented drug interactions deemed clinically significant.

Subgroups

Head-to-head comparison studies did not adequately describe or analyze subgroups for differences in effectiveness, although two assessed differences in adverse effects based on age, gender and race with no differences found. There are studies which suggest that a lower dose of PPI may be equally effective in patients who are older or are deficient in the CYP2C19 liver enzyme (3% of whites and African Americans and 17-25% of Asians). Only one of these studies was a head-to-head comparison, omeprazole versus lansoprazole, but no difference was found between the two. While there may be differing effects of the PPIs based on demographics, there is inadequate data to identify any difference between them.

Table 11: Summary of Evidence

Key Question 1: GERD	Quality of Evidence	Conclusion
esophagitis healing	Good for (o), (l), (r), (p), Good for (e 40mg) vs (o 20mg) Poor for equivalent doses of e vs o. Fair for (e 40 mg) vs (l 30 mg)	8 head-to-head trials and one good quality systematic review found no differences among omeprazole, lansoprazole, rabeprazole, and pantoprazole in healing rates at 4 and 8 weeks. In two trials esomeprazole 40mg had higher 4-week and 8-week healing rates than omeprazole 20mg, but there are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg. One trial of esomeprazole 40 mg versus lansoprazole 30 mg found better healing rates in the esomeprazole group when results were adjusted for severity of illness.
GERD symptoms	Good for (o), (l), (r), (p), Good for (e 40mg) vs (o 20mg) Good for (e 40 mg vs (l 30 mg) Poor for equivalent doses of e vs o Fair for (o 40 mg) vs (l 30 mg)	8 head-to-head trials found no difference in relief of symptoms between omeprazole, lansoprazole, rabeprazole, or pantoprazole. 24 trials of these PPIs compared to H2-RAs, and a previous systematic review also found no differences. A good quality study that measured symptoms and quality of life as primary endpoints found equivalent heartburn relief with omeprazole Multiple Unit Pellet System (MUPS) 20mg and pantoprazole 40 mg, but not with lansoprazole 30 mg. Patient satisfaction at 4 and 8 weeks was equivalent for all 3 PPIs, however. Two studies found esomeprazole at 40mg better at symptom relief than omeprazole 20mg. One good-quality study found better symptom relief on some, but not all, measures for esomeprazole 40 mg compared with lansoprazole 30 mg at 4 weeks and did not measure symptoms at 8 weeks.
GERD relapse	Good for (o), (l), (r) Fair for (e) Poor for (p)	One head-to-head trial[20] of esomeprazole 20 mg or lansoprazole 15 mg found higher remission rates for esomeprazole (83% vs 74%) over 6 months, using life table analysis. Esomeprazole group had higher remission rates across all grades of disease severity, whereas the efficacy of lansoprazole decreased with increasing severity of disease. 2 head-to-head trials found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks and rabeprazole versus omeprazole after 13, 26, and 52 weeks. A systematic review found, in studies comparing PPIs to placebo or ranitidine, similar remission rates for lansoprazole, rabeprazole, and omeprazole over 12 months of treatment. No long-term studies of pantoprazole.
Key Question 2: Ulcer, H. pylori eradication	**Quality of Evidence**	**Conclusion**
Duodenal Ulcer	Good for (l) vs (o) Fair for (p), (r), (e) versus (o)	All newer PPIs have been compared to omeprazole. No significant differences were found. Data from trials comparing PPIs to H2-RAs support this finding. The evidence suggests no difference between the PPIs in healing rates or symptom relief.
Gastric Ulcer	Fair for (r) vs (o) Poor for others	Only one head-to-head study was found, comparing rabeprazole to omeprazole. No significant differences in healing rate, minor improvements in symptom relief with rabeprazole.
NSAID-induced ulcer	Poor	No head-to-head studies. In trials of omeprazole and lansoprazole vs ranitidine, no difference in healing rates or symptom resolution were apparent.
Prevention of NSAID induced ulcer	Poor	No head-to-head studies. In other studies, significant heterogeneity in study design and outcome measure definitions make this evidence insufficient to identify any differences between PPIs.
Eradication of H. pylori	Fair	One fair quality systematic review and 13 more recent trials indicate that eradication rates among the PPIs do not differ significantly. Differences between the antibiotic regimens, participants and study designs limit the strength of this evidence.

Key Question 3: Adverse events	**Quality of Evidence**	**Conclusion**
Long-term studies	Poor	Three comparative trials. Evidence from single-drug followup studies indicates no differences between the PPIs. No long-term studies of esomeprazole or pantoprazole were found.
Short-term studies	Fair	Evidence from short-term head-to-head comparison trials do not indicate a difference in the rate of overall adverse events, serious adverse events or the rate of drop outs due to adverse events. These studies are very short-term and include highly selected patient populations, evidence may not be generalizable to patients with co-morbidities and longer-term treatment.
Drug Interactions	Fair	No head-to-head trials assessing clinically important drug interactions of PPIs in patients with acid-related diseases were found. Based on primarily uncontrolled studies in healthy subjects, omeprazole has more drug interactions than the newer drugs. However, the numbers of drugs with clinically significant interactions are few and monitoring for needed dose adjustments is the only action required.
Key Question 4: Subpopulations	**Quality of Evidence**	**Conclusion**
	Poor	No head-to-head trials of two PPIs assessing the impact of race, age, gender, co-morbidities or other drugs were found. One head-to-head trial of lansoprazole and omeprazole in rapid and slow metabolizers (all Japanese patients) found no difference between these drugs in H. pylori eradication rates. There is insufficient evidence to indicate a difference between the PPIs based on subpopulation characteristics.

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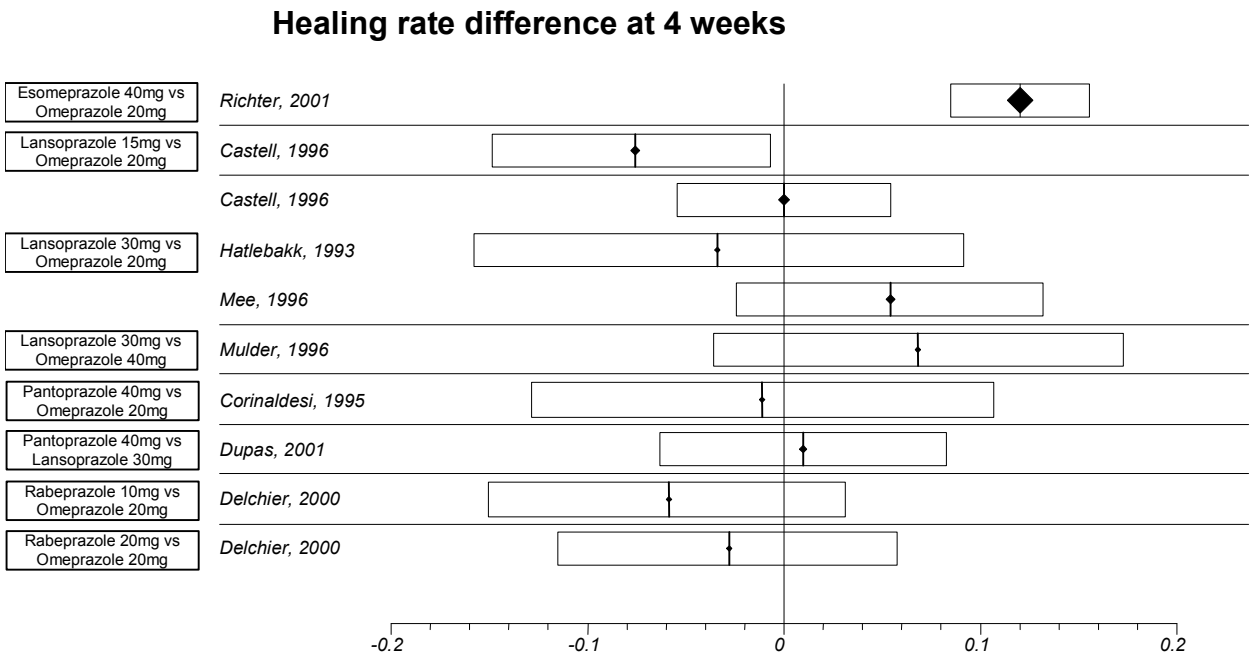
Figure 1. Esophagitis healing rates at 4 and 8 weeks: PPI vs PPI (% risk difference)



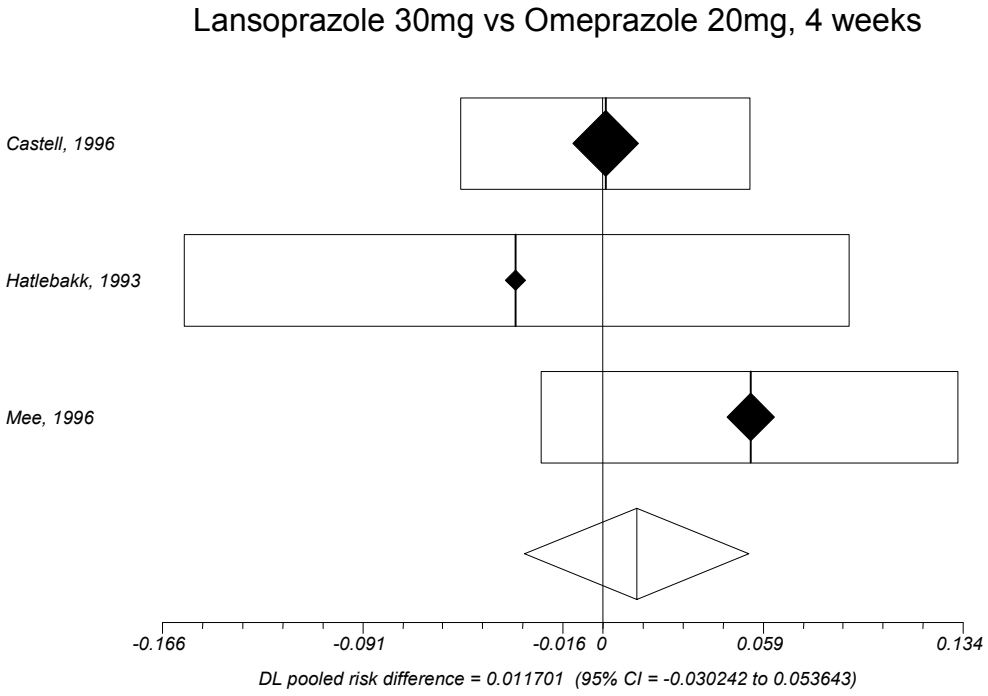
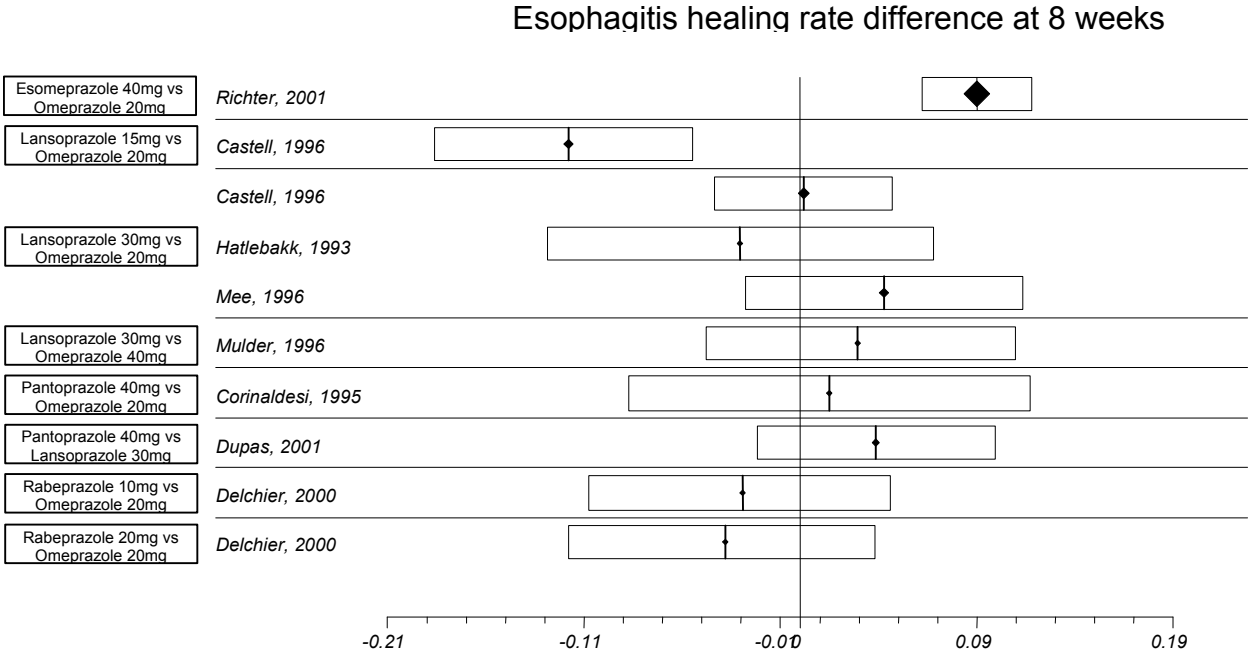


Figure 1 (continued)

Esophagitis Healing at 4 Weeks

Study	Risk difference (%) (95% CI)
esomeprazole 40mg vs omeprazole 20mg once daily	
Richter, 2001	12.0 (8.5, 15.6)
lansoprazole 15mg vs omeprazole 20mg once daily	
Castell, 1996	-7.6 (-14.6, -0.5)
lansoprazole 30mg vs omeprazole 20mg once daily	
Castell, 1996	0.00 (-5.4, 5.4)
Hatlebakk, 1993	-3.4(-15.9, 19.1)
Mee, 1996	5.4 (-2.4, 13.2)
	Pooled risk difference = 1.17 (95% CI -3.02, 5.36)
lansoprazole 30mg vs omeprazole 40mg once daily	
Mulder, 1996	6.8 (-3.4, 17.0)
pantoprazole 40mg vs omeprazole 20mg	
Corinaldesi, 1995	-1.1 (-12.9, 10.7)
pantoprazole 40mg vs lansoprazole 30mg	
Dupas, 2001	1.0% (-6.3, 8.2)
rabeprazole 10mg vs omeprazole 20mg	
Delchier, 2000	-5.8 (-14.6, 2.9)
rabeprazole 20mg vs omeprazole 20mg	
Delchier, 2000	-2.8 (-11.0, 5.4)

Figure 1 (continued)



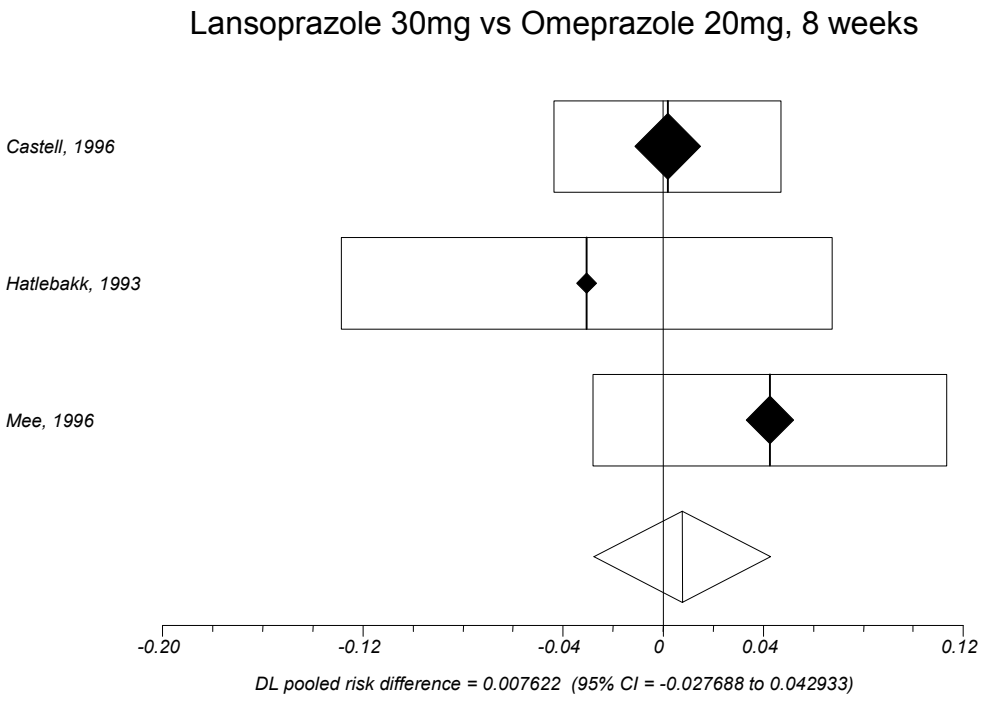
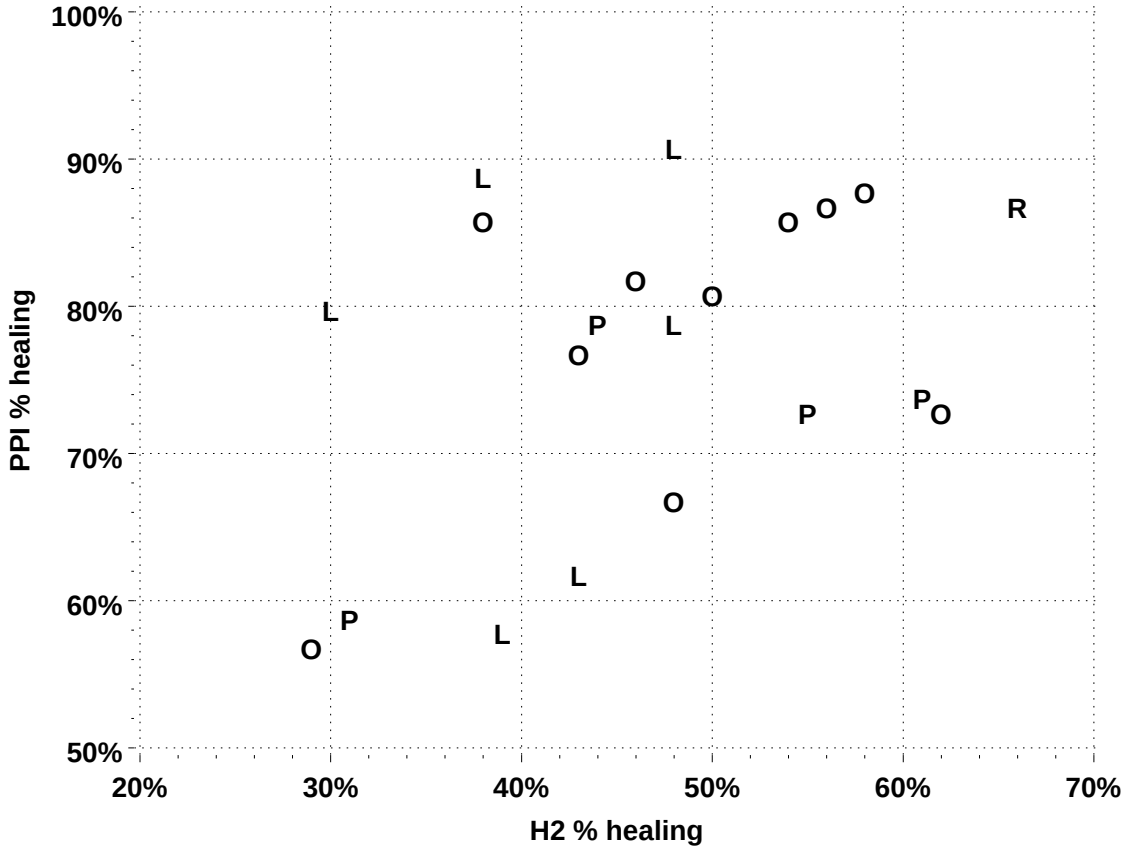


Figure 1 (continued)

Esophagitis Healing at 8 Weeks

Study	Risk difference (%) (95% CI)
esomeprazole 40mg vs omeprazole 20mg once daily	
Richter, 2001	9.0 (6.2, 11.8)
lansoprazole 15mg vs omeprazole 20mg once daily	
Castell, 1996	-11.8(-18.3, -5.2)
lansoprazole 30mg vs omeprazole 20mg once daily	
Castell, 1996	0.02 (-4.3, 4.7)
Hatlebakk, 1993	-3.1(-12.7, 6.6)
Mee, 1996	4.3 (-2.8, 11.3)
	Pooled risk difference = 0.76 (95% CI -0.02, 4.29)
lansoprazole 30mg vs omeprazole 40mg once daily	
Mulder, 1996	2.9 (-4.4, 10.3)
pantoprazole 40mg vs omeprazole 20mg	
Corinaldesi, 1995	1.5 (-8.6, 11.6)
pantoprazole 40mg vs lansoprazole 30mg	
Dupas, 2001	3.9% (-2.1, 9.8)
rabeprazole 10mg vs omeprazole 20mg	
Delchier, 2000	-2.9 (-10.0, 4.2)
rabeprazole 20mg vs omeprazole 20mg	
Delchier, 2000	-3.8 (-11.0, 3.5)

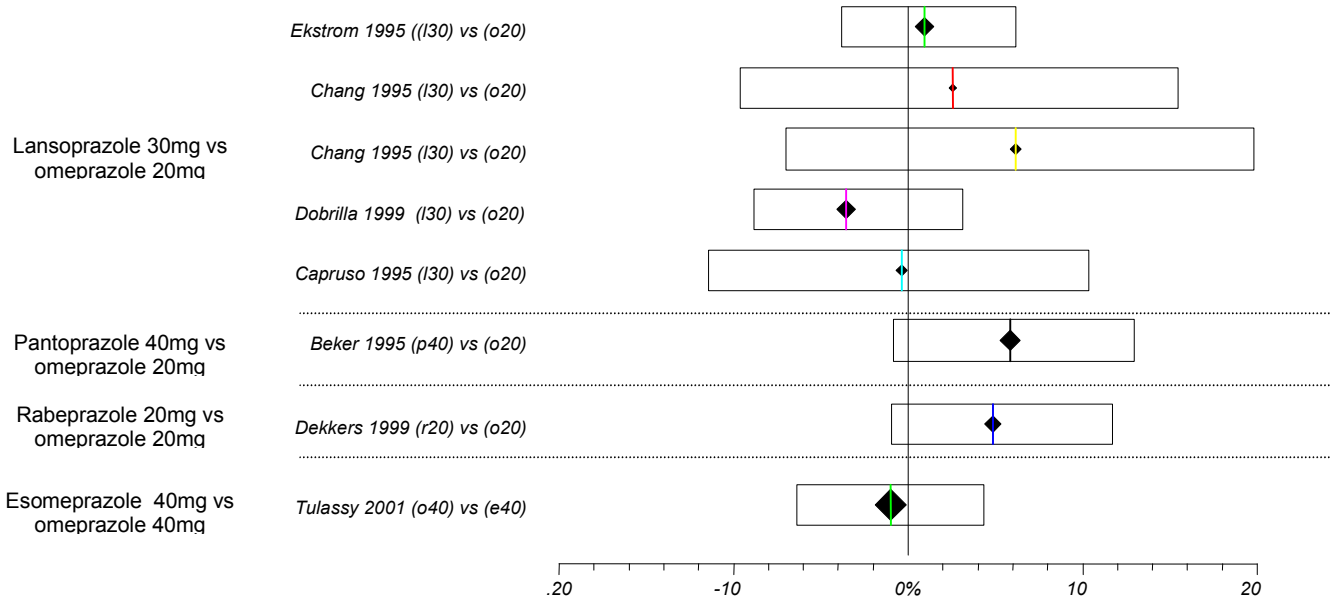
Figure 2. PPI vs. H2 Receptor antagonists for esophagitis healing at 8 weeks.



Estimated healing rate	Mean	95% CrI	
Lansoprazole	78.8%	69.7%	86.4%
Omeprazole	79.3%	72.2%	85.3%
Pantoprazole	71.2%	59.0%	81.4%
Rabeprozole	85.6%	67.9%	95.4%

Difference between PPIs	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	-0.5%	-11.6%	10.0%
Lansoprazole vs Pantoprazole	7.5%	-5.9%	22.1%
Lansoprazole vs Rabeprazole	-6.9%	-20.5%	12.2%
Omeprazole vs Pantoprazole	8.1%	-4.3%	21.7%
Omeprazole vs Rabeprazole	-6.4%	-18.9%	12.2%
Pantoprazole vs Rabeprazole	-14.4%	-30.4%	5.5%

Figure 3. Duodenal Ulcer Healing at 4 weeks: PPI vs PPI (% risk difference)



Study	Risk difference (%) (95% CI)
Lansoprazole 30mg vs omeprazole 20mg once daily	
Ekstrom 1995	0.96 (-3.80, 6.15)
Chang 1995	2.55 (-9.62, 15.5)
Chang 1995	6.14 (-7.0, 20)
Dobrilla 1999	-3.57 (-8.84, 3.14)
Capruso 1995	-0.34 (-11.41, 10.32)
	Pooled risk difference = -0.2 (95% CI -3.0, 2.6)
Pantoprazole 40mg vs omeprazole 20mg once daily	
Beker 1995	5.85 (-0.84, 12.95)
Rabeprazole 20mg vs omeprazole 20mg once daily	
Dekkers 1999	4.84 (-0.96, 11.70)
Esomeprazole 40mg vs omeprazole 40mg once daily	
Tullassay 2001	-0.97 (-6.4, 4.35)

Figure 4. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks

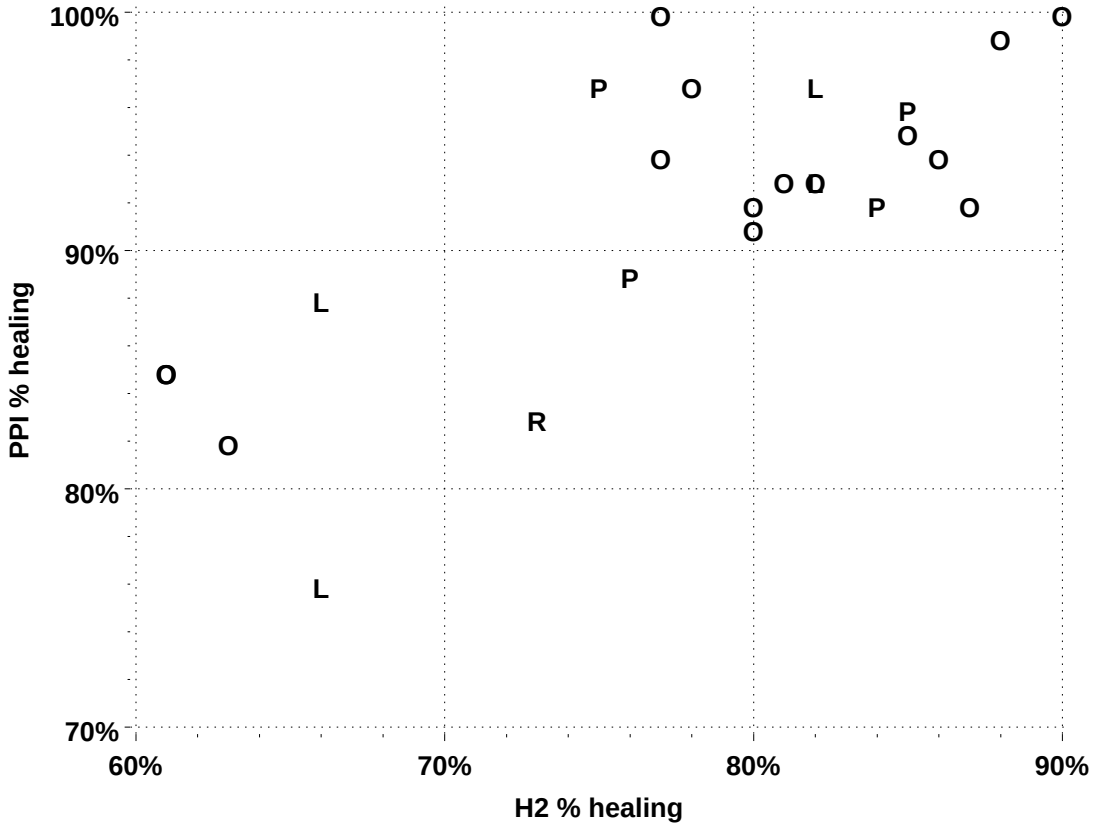


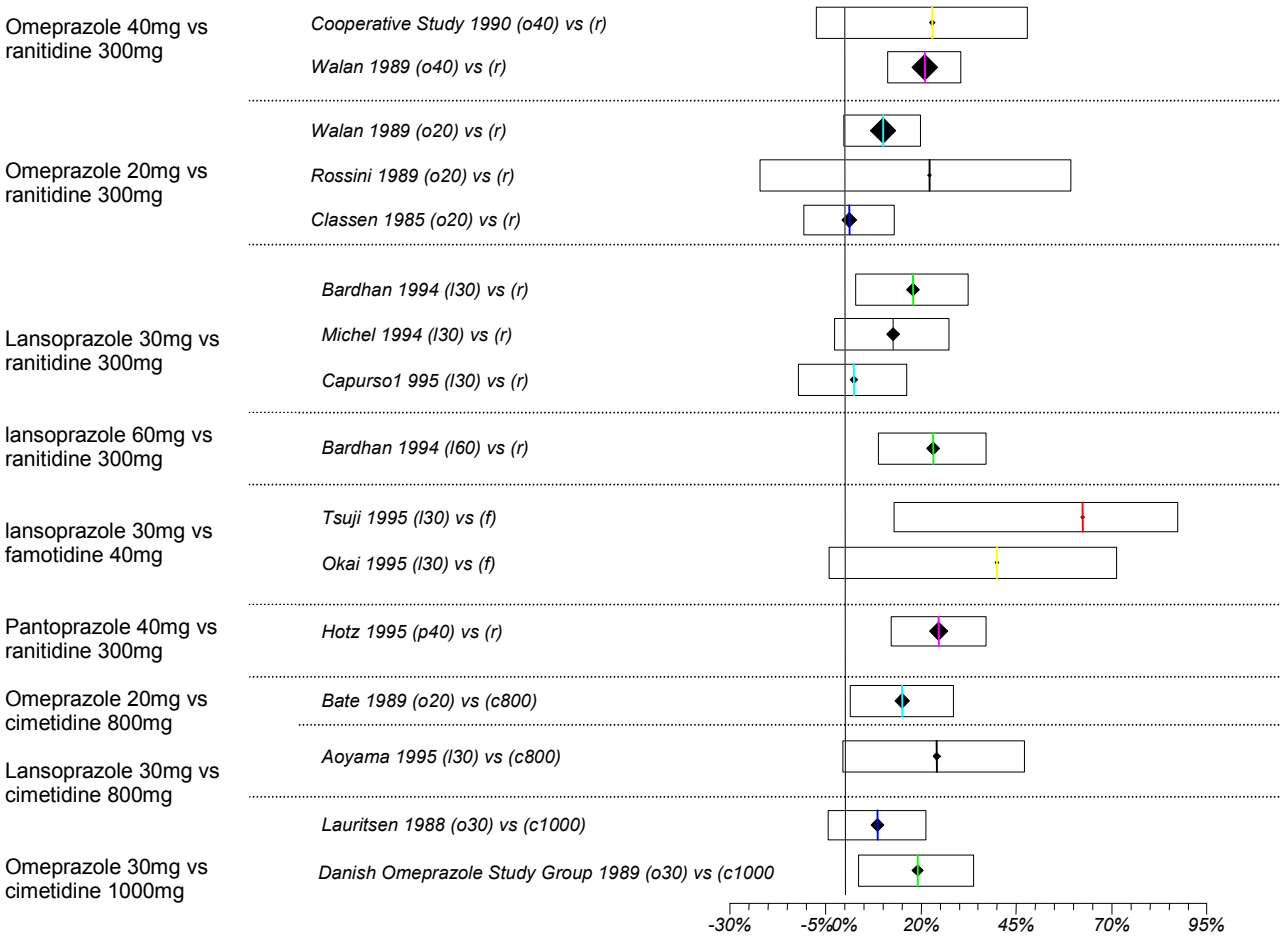
Figure 4 (continued)

Duodenal ulcer healing rate at 4 weeks

Estimated healing rate	when H2 healing is…	Mean	95% CrI	
Lansoprazole	60%	73.3%	55.8%	86.9%
	73%	89.6%	85.0%	93.5%
	80%	93.9%	89.5%	97.1%
	90%	97.0%	92.6%	99.3%
Omeprazole	60%	82.6%	75.5%	88.7%
	73%	90.9%	88.7%	93.1%
	80%	93.7%	91.9%	95.4%
	90%	96.3%	94.5%	97.8%
Pantoprazole	—	93.9%	90.9%	96.2%
Rabeprozole	—	82.6%	70.9%	91.1%

Difference between PPIs	when H2 healing is…	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	60%	-9.3%	-28.1%	6.1%
	80%	0.2%	-4.6%	3.8%
	90%	0.8%	-4.0%	3.8%
Lansoprazole vs Pantoprazole	80%	0.0%	-5.0%	4.4%
Lansoprazole vs Rabeprazole	73%	7.0%	-2.5%	19.3%
Omeprazole vs Pantoprazole	80%	-0.2%	-3.1%	3.3%
Omeprazole vs Rabeprazole	73%	8.3%	-0.2%	20.3%
Pantoprazole vs Rabeprazole	—	11.3%	2.4%	23.2%

Figure 5. Gastric Ulcer: PPI vs H2-Antagonist healing at 4 weeks (% risk difference)



Study	Risk difference (%) (95% CI)
Cooperative Study 1990 (o40) vs(r)	22.92% (-7.50%, 47.83%)
Walan 1989 (o40) vs (r)	21.02%(11.31%, 30.37%)
Walan 1989 (o20) vs (r)	9.97% (-0.19%, 19.92%)
Rossini 1989 (o20) vs (r)	22.22% (-22.28%, 59.36%)
Classen 1985 (o20) vs (r)	1.09% (-10.66%, 12.83%)
Bardhan 1994 (l30) vs (r)	17.82% (2.82%, 32.26%)
Michel 1994 (l30) vs (r)	12.66% (-2.53%, 27.31%)
Capurso1 995 (l30) vs (r)	2.43% (-12.18%, 16.35%)
Bardhan 1994 (l60) vs (r)	23.22% (8.78%, 37.08%)
Tsuji 1995 (l30) vs (f)	62.50% (12.85%, 87.18%)
Okai 1995 (l30) vs (f)	40.00% (-4.08%, 71.22%)
Hotz 1995 (p40) vs (r)	24.67% (12.15%, 37.01%)
Bate 1989 (o20) vs (c800)	15.08% (1.45%, 28.38%)
Aoyama 1995 (l30) vs (c800)	24.06% (-0.38%, 47.17%)
Lauritsen 1988 (o30) vs (c1000)	8.56% (-4.24%,21.27%)
Danish Omeprazole Study Group 1989 (o30) vs (c1000mg)	19.07% (3.49%, 33.82%)

Figure 6. NSAID-induced Gastric Ulcer healing Rates at 8 weeks (% risk difference)

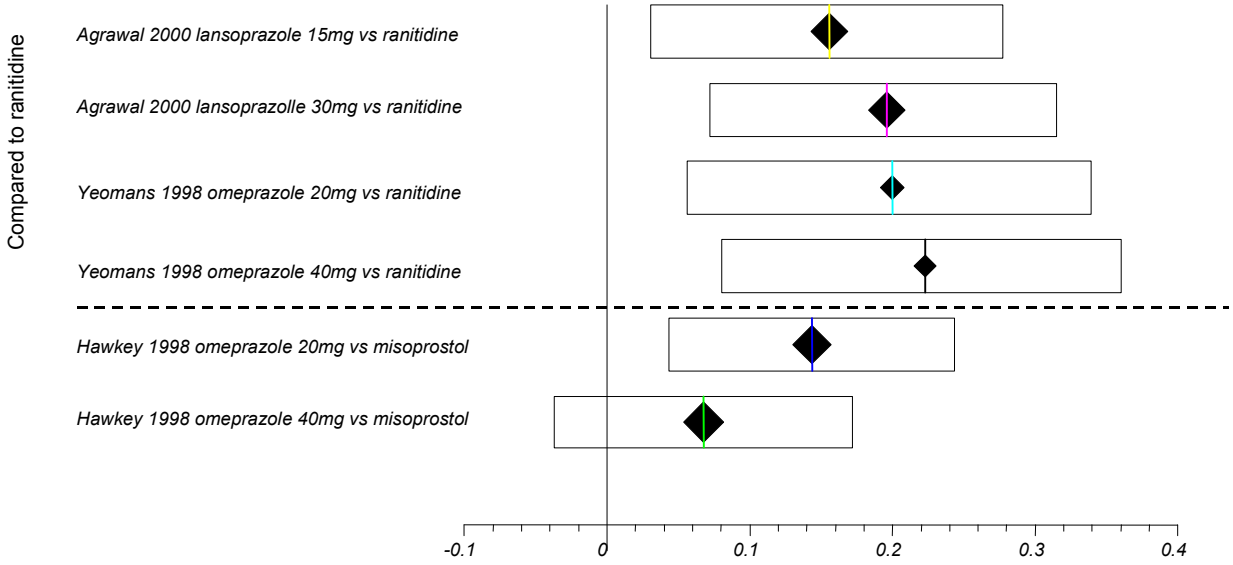


Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Castell et al. 2002	5241 patients, multiple centers, mean age 47 (range 18-75), 57% male, 91% white, 6% black, 3% other.	LA Grade A: 36% B: 40% C: 18% D: 6% Heartburn Severity None: 1% Mild: 10% Moderate: 47% Severe: 42%	5241 enrolled, ITT Number screened NR (l) 30 mg (n=2617) (e) 40 mg (n=2624)	(e) 79.4% (l) 75.1% (p≤.001) (life-table analysis) (e) 75.7% (l) 71.7% (p≤0.01, stratified by baseline severity)	EE (e) 92.6% (l) 88.8% (p=.0001) (life-table analysis) (e) 87.6% (l) 84.2% (p<0.01, stratified by baseline severity)
Castell 1996	1070 US patients at multiple centers (number excludes placebo), mean age 47, (range 18-84); 60-68.4% male; 85% white, 9% black, 5% Hispanic.	Grade 2: 61%-71% Grade 3: 24%-30% Grade 4: 6%-9% (See Appendix E for scale) 6.5%-8.7% Barrett's esophagus	1284 enrolled, 1226 analyzed (total with placebo)	(l)15: 72.0% (l)30: 79.6% (o)20: 87.0% (l)30 vs (l)15 p<.05 (o)20 vs (l)15 p<.05 Other comparisons NS	(l)15: 75.2% (l)30: 87.1% (o)20: 87.0% (l)30 vs (l)15 p<.05 (o)20 vs (l)15 p<.05 Other comparisons NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Castell et al. 2002	*Complete resolution of heartburn:* (l) 60.2% (e) 62.9% (p≤.05) *Heartburn-free nights:* (l) 85.8% (e) 87.1% (p≤.05) *Heartburn-free days:* NS	NR	No difference in treatment-related adverse effects. Withdrawal due to adverse event 1.8% vs. 1.9%.	Good	Supported by AstraZeneca, also listed in author credits
Castell 1996	Not given	*Median percentage of days with heartburn:* (l)15: 12.3% (l)30: 8.6% (o)20: 11.8% *Median percentage with heartburn:* (l)15: 9.3 (l)30: 6.5 *(not ITT)* (l)15 vs (o)20 p<0.05 nights (l)15 vs (l)30 p< days and nights All other comparisons NS	(o)20: 2% (l)30: 1.7% (l)15: 0.9%	Fair: randomization and allocation method not reported, attrition not reported	Supported by TAP Pharmaceuticals, Inc.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Hatlebakk 1993	229 patients at 9 hospitals in Norway and Sweden; mean age 55; 66% male; ethnicity not given	(l)30 group: Grade 0: 2.6% Grade 1: 34.5% Grade 2: 50.9% Grade 3: 12.1% (o)20 group: Grade 0: 2.7% Grade 1: 38.9% Grade 2: 55.8% Grade 3: 2.7% (See Appendix E for scale)	Number screened not given, 229 enrolled.	(l)30: 61.2% (o)20: 64.6% p=NS	(l)30: 81.9% (o)20: 85.0% p=NS
Mee 1996	604 patients at multiple centers, UK and Ireland, mean age 53; 67% male; ethnicity not given.	Grade 1: 39% Grade 2: 44% Grade 3: 15% Grade 4: 2% (Savary-Miller)	604 enrolled, 565 eligible, 537 evaluable	(l)30: 62% (o)20: 56.6% p=NS	(l)30: 75.3% (o)20: 71.1% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Hatlebakk 1993	Data not given: states (l)30 had greater improvement in heartburn (p=0.03)	Data not given, but states no significant differences in any symptoms.	(o)20: 0.9% (l)30: 0	Poor: randomization and allocation method not reported, no intention-to-treat analysis, eligibility criteria not specified, some differences at baseline.	Not reported
Mee 1996	Not given	*Improvement in daytime epigastric pain* (l)30: 85.9% (o)20: 72.5% *Improvement in nighttime epigastric pain* (l)30: 85.9% (o)20: 67.3% p=NS (includes only pts who attended 8-week visit who reported baseline pain)	Not reported	Good/Fair: Allocation concealment method not given.	1 of 2 authors from Lederle Laboratories, funding info not given.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Mulder 1996	211 patients at multiple centers in The Netherlands; mean age 55; 70% male; ethnicity not given.	Grade 1: 0.47% (1 patient) Grade 2: 68% Grade 3: 24% Grade 4A: 8% (Savary-Miller)	Number screened not given, 211 enrolled, 3 lost to followup, 3 withdrew for lack of efficacy, 1 withdrawn for receiving double dose.	(l)30 ITT 85.50% PP 86.20% (o)40 ITT 79% PP 79.6% p=NS	(l)30 ITT: 93.40% PP 95.70% (o)40 ITT: 90.50% PP 93.4% p=NS
Mulder et al. 2002	461 patients, multiple centers Mean age 51.2 (range 18-80) 59% male Ethnicity NR	Savary-Miller class: I: 59% II: 29% III: 8% IVa: 4% Heartburn Severity None: 4% Mild: 22% Moderate: 45% Severe: 29%	461 enrolled Number screened NR ome 20 mg (n=151) lan 30 mg (n=156) pan 40 mg (n=154)	NR	NR

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Mulder 1996	(l)30 No symptoms: ITT: 73.60% (o)40 No symptoms: ITT 71.40%	"Because of the low number of patients not healed at 4 weeks, analysis of symptoms was not performed at 8 weeks."	None	Fair: randomization and allocation concealment not reported,	Supported by Hoechst Marion Roussel BV and Janssen-Cilag BV, Netherlands
Mulder et al. 2002	(ome vs lan vs pan) Heartburn relief : 84% vs. 78% vs. 84% ome vs lan 90% CI -1.44 to 13.24 pan vs lan 90% CI -1.07 to 13.49 Satisfied: 79% vs. 76% vs. 79%. ome vs lan 90% CI -4.04 to 11.68 pan vs lan 90% CI -4.94 to 10.80 pan vs ome 90% cI -4.12 to 7.13	(ome vs lan vs pan) Heartburn relief : 87% vs. 81% vs. 89% pan vs ome 90% CI -4.55 to 7.64 ome vs lan 90% CI -0.79 to 12.81 pan vs lan 90% CI 0.94 to 14.17 Satisfied: 89% vs. 86% vs. 91% ome vs lan 90% CI -2.68 to 9.69 pan vs lan 90% CI -0.97 to 10.99 pan vs ome 90% CI -4.12 to 7.13	No difference in AEs between groups. None considered treatment related. Total withdrawals due to AE: 6/461 (1.3%) Total AEs: 73/461 (15.8%)	Fair: randomization and allocation methods not reported. More withdrawals in L group.	Supported by AstraZeneca

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Dekkers 1999	202 patients of 27 investigators in 10 European countries, mean age 53 + 15.63, (range 20-86); 62% male; ethnicity not given.	Grade 2: 43% Grade 3: 52% Grade 4: 4% (modified Hetzel-Dent)	Number screened not given, 202 enrolled, 192 completed.	(r)20: 81% (o)20: 81% (Not ITT) p=NS	(r)20: 92% (o)20: 94% (Not ITT) p=NS
Delchier 2000	300 patients of 61 investigators at 50 European centers, mean age 53 (+15), (range 18-80); 62% male; ethnicity not given.	Mean grade 2.6-2.7, median 3.9, (modified Hetzel-Dent) 7% had Barrett's esophagus, 41% positive for H. pylori	358 screened, 310 randomized, 298 completed.	(r)20: 88.5% (r)10: 85.4% (o)20: 91.2% p=NS	(r)20: 91.3% (r)10: 91.3% (o)20: 94.2% p=NS
Kahrilas 2000	1960 US patients at 140 centers; mean age 46; 60% male; ethnicity not given.	Grade A: 33% Grade B: 40% Grade C: 19% Grade D: 5% (Los Angeles classification) 9.6% H. pylori	3354 screened, 1960 randomized. 44 did not complete study due to an adverse event and 115 for other reasons including loss to f/u and withdrawal of consent.	(e)40: 75.9% (e)20: 70.5% (o)20: 64.7% (cumulative life table rate) (e)20 vs (o)20 p=0.09 (e)40 vs (o)20 "significantly" higher (p not given)	(e)40: 92.2% (e)20: 89.9% (o)20: 86.9% (cumulative life table rate) (e)40 vs (o)20 p<0.001 (e)20 vs (o)20 p<0.05

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Dekkers 1999	*Heartburn frequency (resolution):* (r)20: 29.6% (o)20: 26.5% *Daytime severity (resolution):* (r)20: 61.9% (o)20: 60.8% *Nighttime severity resolution:* (r)20: 61.6% (o)20: 57.3% p=NS for all	*Heartburn frequency resolution:* (r)20: 37.8% (o)20: 31.4% *Daytime severity resolution:* (r)68.0% (o)20: 66.0% *Nighttime severity resolution:* (r)20: 64.4% (o)20: 66.7% p= NS for all	(r)20: 1% (o)20: 0	Fair: randomization and allocation method not reported intention-to-treat for symptoms only, not for healing.	Last author (corresponding author) and 5th authors with Eisai Ltd, funding info not given.
Delchier 2000	*Severity of daytime and nighttime heartburn:* p=NS (numbers not given)	*Severity of daytime and nighttime heartburn:* p=NS (numbers not given)	(r)10: 5% (r)20: 5% (o)20: 2%	Fair: randomization and allocation method not reported, followup somewhat high (76%-83%).	Funded by Eisai Ltd, London, last author (corresponding author) from Eisai
Kahrilas 2000	*Resolution of heartburn* (e)40: 64.7% (e)20: 61.0% (o)20: 57.2% (e)40 vs (o)20 p=0.005 other comparisons NS	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"	(e)40: 2% (e)20: 2.6% (o)20: 2%	Fair: Randomization method not reported, intention-to-treat for symptoms only, not healing, baseline characteristics not analyzed, more dropped for "other" reasons in (o) groups, more for adverse events in (e)20 group (18 vs 13).	4 of 9 authors from Astra Zeneca, study supported by grant from Astra Zeneca.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Richter 2001	2425 patients at 163 US centers; mean age 47 (sd 12); 61% male; ethnicity not given.	Grade A: (e)40 35%; (o)20 32% Grade B: (e)40 39%; (o)20 42% Grade C: (e)40 21%; (o)20 20% Grade D: (e)40 5%; (o)20 7% (LA classification)	4798 screened, 2425 randomized; 109 did not complete: 24 for adverse events, 25 investigator-initiated decision, 25 lost to followup, 31 consent withdrawn, 4 lack of therapeutic response.	(e)40 ITT 78.60% cumulative life table rate 93.70% (o)20 ITT 66.60% cumulative life table rate 83.20%	ITT 89.90% cumulative life table rate 93.70% ITT 80.90% cumulative life table rate 84.20%
Corinaldesi 1995	241 patients at 30 centers, Belgium, France, Italy, the Netherlands, median age 50-52, (range 18-88); 63% male; ethnicity not given.	Grade 2: 82% Grade 3: 18% (Savary-Miller)	Number screened not given, 241 randomized, 208 evaluable; 3 withdrew, 23 did not attend f/u.	(p)40: 67.5% (o)20: 68.6% p=NS	(p)40: 80.8% (o)20: 79.3% p=NS
Dupas 2001	461 patients at 29 hospital centers and 45 private practices in France; mean age 54 (±14.6); 74% male; ethnicity not given	83% Grade 2 17% Grade 3 (Savary-Miller)	Number screened not given; 461 randomized, 385 completed	(p)40 ITT: 80.90% (l)30 ITT: 80% p=NS	(p)40 ITT: 89.80% (l)30 ITT: 90% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Richter 2001	(e)40 resolution of heartburn: 68.30% (o)20 resolution of heartburn: 58.10%	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"	1% in each group	Good	Supported by Astra Zeneca, one or more authors from Astra Zeneca.
Corinaldesi 1995	*Heartburn free:* (o)20: 82.2% (p)40: 87.9% p=NS	Not reported	(p)40: 0.8% (o)20: 1.7%	Poor: randomization and allocation method not reported, no intention-to-treat analysis, baseline characteristics not analyzed.	Last author from Byk Gulden Pharma-ceuticals, study supported by same.
Dupas 2001	*Symtom free (all symptoms - heartburn, acid regurgitation, pain or swallowing):* ITT: (p)40: 83% (l)30: 92% p=NS	Not reported	(p)40: 13% (l)30: 2.5%	Fair: randomized method not clear, allocation method not reported	Funded by BYK France, last author from BYK

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 3. Randomized controlled trials of GERD relapse prevention: PPI vs PPI

Author, Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Lauritsen et al. 2003	1224 patients in Europe and South Africa with history of heartburn and endo-verified GERD. Mean age: 49 Male: 61% White: 98%	LA grade A: 38% B: 45% C: 14% D: 3% H. pylori positive: 31%	1391 enrolled in healing phase, 1236 (89%) randomized for maintenance treatment. ITT = 1224 (615(e), 609(l)). Healing phase: 31/1391 (2.2%) withdrawn for AE; 63 (4.5%) lack of therapeutic response; 61 (4.4%) lost, excluded, other. Randomized pop. exclusion: 12/1236 (0.1%) excluded from ITT for noncompliance or persistent esophagitis at entry. Maintenance phase: 51/1236 (4.1%) withdrawn for AE; 124 (10.0%) lack of therapeutic response; 50 (4.0%) lost, other. Similar AE profiles between groups.
Thjodleifsson, 2000	243 patients at 21 centers in Europe with a previous diagnosis of erosive GERD healed within 90 days of enrollment; mean age 52.7 (+/- 14.3); 67% male; ethnicity not given.	Grade 0: 77% Grade 1: 22% 1 missing (modified Hetzel-Dent)	210/243 completed. 13 withdrew for adverse events.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Table 3. Randomized controlled trials of GERD relapse prevention: PPI vs PPI (continued)

Author, Year	Results	Quality rating	Funding source and role of funder
Lauritsen et al. 2003	*Endoscopic remission at 6 months.* (e) 84% vs. (l) 76% (p<.0002)	Fair: small differences at baseline (slightly > males on Eso, slightly more H. pylori positive on Lan); not ITT: 12 randomized but not included in ITT analysis for not taking any study drug OR persistant esophagitis at baseline (combined); 4 in Eso group, 8 in Lan group	Sponsored by AstraZeneca
Thjodleifsson, 2000	*Endoscopic relapse at 13 weeks:* (r)10: 1.2% (r)20: 2.6% (o)20: 1.2% *Endoscopic relapse at 26 weeks:* (r)10: 1.2% (r)20: 3.8% (o)20: 1.2% *Endoscopic relapse at 52 weeks:* (r)10: 4.9% (r)20: 3.8% (o)20: 4.8% p=NS for all comparisons	Fair: allocation concealment not reported, not clear if maintenance of comparable groups.	Not reported. Last author (corresponding author) from Eisai, Inc.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Table 3. Randomized controlled trials of GERD relapse prevention: PPI vs PPI (continued)

Author, Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Carling, 1998	248 patients at 23 centers in Denmark, Finland, and Sweden; mean age 56 (+/- 12); 62% male; ethnicity not given	Grade 2: 72% Grade 3: 22% Grade 4: 6% (Savary-Miller)	289 treated , 262 healed, 248 continued to maintenance phase, 226 included in per protocol analysis.
Jasperson, 1998	30 patients in Germany whose esophagitis healed after 6-8 weeks of omeprazole; mean age 57; 60% male; ethnicity not given.	All Grade 4 (Savary-Miller)	36 treated, 6 did not heal, 30 included.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Table 3. Randomized controlled trials of GERD relapse prevention: PPI vs PPI (continued)

Author, Year	Results	Quality rating	Funding source and role of funder
Carling, 1998	*Endoscopic relapse by 48 weeks:* (l)30: 8.7% (o)20: 8.2% *Symptomatic relapse by 48 weeks:* (l)30: 0.8% (o)20:1.6% p=NS	Fair: allocation concealment not reported, more excluded from lansoprazole group at entry, more Grade 2 in lansoprazole group at baseline.	Supported by Wyeth Ayerst and Wyeth Lederle.
Jasperson, 1998	*Endoscopic remission at 4 weeks:* (o)20: 90% (l)30: 20% (p)40: 30% *Recurrence of reflux symptoms at 4 weeks:* (o)20: 10% (l)30: 60% (p)40: 60% (o) vs (l) p<0.01 (o) vs (p) p<0.01	Fair: allocation concealment not reported, blinding of patients not reported, very small sample size. There was selection bias.	Not reported.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive	Lansoprazole 30mg once a day x 4 weeks, then those with healed ulcer randomized to 15 or 30mg lansoprazole daily x 12 months	Omeprazole 40mg once a day, then those with healed ulcer switched to omeprazole 20mg daily x 12 months	251 eligible (167 (l), 84 (o)), unclear number found H. pylori positive who decided not to participate. Maintenance phase: 243 enrolled (164 (l), 79(o))
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	Not available	Lansoprazole 30mg once daily x 4 weeks	Omeprazole 20mg once daily x 4 weeks	111 enrolled (57 (l), 54 (o))
Capurso 1995 Italy multicenter	Reported as 'balanced' for age, sex, weight, smokers, alcohol use, ulcer history, symptoms, ulcer size, and prior complications	Lansoprazole 30mg a day (morning) x 2 to 6 weeks	Omeprazole 20mg once daily x 2 to 6 weeks	107 enrolled, (52 (l), 55(o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI (cont.)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dobrilla 1999 Italy Multicenter	***Healing:*** *4 weeks:* (unclear analysis, only 243 of 251 included) 93.9% (l), 97.5% (o) ***PP analysis (# not reported):*** *4 weeks:* 99% (l), 100% (o) ***Symptoms:*** *No pain at 4 weeks:* 87.9% (l), 87.4% (o) ***Maintenance:*** (unclear analysis) *6 months:* 4.5% (l15), 0% (l30), 6.3% (o) relapse *12 months:* 3.3% (l15), 0% (l30), 3.5% (o) ***PP analysis:*** *6 months:* 0% relapse in all groups *12 months:* 1.9% (l15), 0% (l30), 3.6% (o) relapse *Followup (at 18 months):* 27.3% (l15), 20%(l30), 26.7% (o) relapse	16 during phase I (4 weeks), 10 (6%, l), 6 (7.1%, o) Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o). The most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 l15, 2 l30, 3 o) including diarrhea, rash, gynecomastia, asthenia, precordial pain, fever, and weight gain. No significant changes in laboratory tests were found. Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) group had the least and the (l30) group had the highest elevation at 6 and 12 months. At 6 months followup all values were returning to baseline.	Fair-poor
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	***Healing:*** *4 weeks:* (ITT) 89.5% (l), 83% (o) (PP) 96% (l), 94% (o)	Hypergastrinemia in both groups (approximately 1.6 fold increase) Skin rash and constipation occurred in a few cases (groups not specified)	Not assessed
Capurso 1995 Italy multicenter	***Healing rates:*** *2 weeks:* 58% (l), 57% (o) *4 weeks:* 94% (l), 94% (o) ***Nighttime pain free:*** *2 weeks:* 94% l), 87% (o) (NS) ***Daytime Pain free*** *2 weeks:* 92% (l), 81% (o) (NS)	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Ekstrom 1995 Sweden Multicenter	Mean age 55 47% smokers 43% alcohol users 10% NSAID users	Lansoprazole 30mg once a day x 4 weeks	Omeprazole 20mg a day x 4 weeks	279 enrolled (143 (l), 136 (o))
Fanti 2001 Italy Single center	Median age 47 (l) and 48 (o) 68% male 56% smokers 54% alcohol users	Lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	Omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))
Chang 1995 Taiwan Single center	Mean age 57 and 61 89% male 47% smokers 93% H. pylori positive	Lansoprazole 30mg once daily x 4 weeks	Omeprazole 20mg once daily x 4 weeks	83 enrolled (42 (l), 41 (o))
Dekkers 1999 Belgium, England, Germany Multicenter	Mean age 48 (range 20-77) 65% male 51% smokers 54% alcohol users 83% H. pylori positive	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing.	Omeprazole 20mg a day x 4 weeks (Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing.)	205 enrolled (102 (r), 103 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI (cont.)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Ekstrom 1995 Sweden Multicenter	***Healing rates:*** *2 weeks:* Endo: 86.2% (l), 82.1% (o) PPI: 87.9%(l), 82.3 (o) *4 weeks:* Endo: 97.1% (l), 96.2% (o) PPI: 97.7% (l), 96/7% (o) ***Symptoms:*** Most patient's symptoms improved to 'occasional' or 'none' by two weeks, nearly all by 4 weeks in both groups. At 4 weeks the reduction in symptoms favored lansoprazole, p = 0.041 (98% vs 96% with more than occasional symptoms). *Antacids:* no difference found	68 adverse events occurred in 57 patients (23 patients taking (l), 34 taking (o)). No statistically significant difference in the severity was found between the two groups. A statistically significant difference was found in the mean change in ALAT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o)).	Fair
Fanti 2001 Italy Single center	***Healing rates:*** *8 weeks:* 100% both groups ***Symptoms:*** " rapid clinical response with disappearance of symptoms in both groups"	"Mild and self-limiting" Total number not reported 1 (l) stomatitis and 1 (o) mild diarrhea	Fair
Chang 1995 Taiwan Single center	***Healing:*** *4 weeks:* 95.2% (l), 92.7% (o) ***H. Pylori eradication:*** *4 weeks:* 78.9% (l), 82.1% (o)	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication (of those H. pylori positive)	Fair
Dekkers 1999 Belgium, England, Germany Multicenter	***Healing rates*** (ITT): *2 weeks:* 69% (r), 61% (o) *4 weeks:* 98% (r), 93% (o) ***Healing rates*** (Endo): *2 weeks:* 69% (r), 63% (o) *4 weeks:* 99% (r), 96% (o) ***Pain frequency:*** all patients showed improvement (no statistical difference found) ***Pain severity:*** All patients reported improvement in both daytime and nighttime pain. The only statistically significant difference was found in daytime pain at 4 weeks (92% vs 83% improved, (r) vs (o), p = 0.038). No difference found in the number pain free.	43 patients reported at least on adverse event. (21 (r), 22 (o)). The most common was headache. The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).	Fair

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Beker 1995 Multicenter	Median age 44 (range 20 - 86) 70% male 50% smokers 20% alcohol users 58% 2 or more previous ulcers	Pantoprazole 40mg once daily x 2 to 4 weeks	Omeprazole 20mg once daily x 2 to 4 weeks	270 enrolled (135 each group)
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	Mean age 49 (SD 13) 62% male 100% white 57% smokers all were H. pylori positive	Esomeprazole 40mg plus clarithromycin 500mg and amoxicillin 1gm x 1 week, placebo x 3 weeks	Omeprazole 40mg x 4 weeks plus clarithromycin 500mg and amoxicillin 1gm x 1 week	446 randomized (222 (e) 224 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI (cont.)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Beker 1995 Multicenter	**Healing:** (PP analysis) *2 weeks:* 71% (p), 65% (o) (p=0.31) *4 weeks:* 95% (p), 89% (o) (p= 0.09) ITT analysis results reported as 'similar' ***Symptoms:*** Pain free (of those with pain at baseline) *2 weeks:* 81% (p), 82% (o) (p = 0.87) *Patient diary:* no significant differences in time course of becoming pain free.	21 patients reported adverse events (10 (p), 11 (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), 4 (o)). 3 in the (o) group were considered possibly related to study treatment (1 angina pectoris, 1 hypertension, 1 vertigo) and patients were withdrawn from study. The other 2 were GI hemorrhage (p), and abdominal pain (o) and considered not related to study drugs. No clinically significant changes in lab values from baseline values. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	***Healing rates:*** *4-6 weeks:* (ITT) 91% (e), 92% (o) (PP) 94% (e), 96% (o) H. pylori eradication: (ITT) 86% (e), 88% (o) (PP) 89% (e), 90% (o) (NS)	33% of (e) and 29.5% of (o) reported at least one adverse event. Most frequent taste perversion, diarrhea, loose stools. 4 discontinued for adverse events (e: 1 for taste perversion/vomiting, o: 1 for rash, 1 allergic reaction, 1 dysmenorrhea). No clinically relevant trends for changes in laboratory safety variables.	Fair

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive 21% NSAID users80% treated with (l) x 8-16 weeks for acute ulcer 95% H-2 antagonist resistant acute ulcer	Lansoprazole 15 or 30mg daily x 12 months	Omeprazole 20mg daily x 12 months	Maintenance phase: 243 enrolled (164 (l), 79(o))
Lanza 1997 USA Multicenter	Mean age 43 63% male 76% Caucasian 48% smokers 56% alcohol users	Lansoprazole 15mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled (88 (pl), 92 (l))
Kovacs 1999 USA Multicenter	Mean age 57 (pl), 54 (l15), 47 (l30) 88% male 57% smokers 39% alcohol users	Lansoprazole 15 or 30mg once daily for up to 12 months	Placebo once daily for up to 12 months	19 (pl), 18 (l15), 19 (l30), other 3 not reported)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Dobrilla 1999 Italy Multicenter	***Maintenance:*** (unclear analysis) *6 months:* 4.5% (l15), 0% (l30), 6.3% (o) relapse *12 months:* 3.3% (l15), 0% (l30), 3.5% (o) ***PP analysis:*** *6 months:* 0% relapse in all groups *12 months:* 1.9% (l15), 0% (l30), 3.6% (o) relapse *Followup (at 18 months):* 27.3% (l15), 20%(l30), 26.7% (o) relapse	Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) group had the least and the (l30) group had the highest elevation at 6 and 12 months. At 6 months follow up all values were returning to baseline.	Fair/poor	If assigned to (l) during treatment study, randomized to (l); if assigned to (o) for treatment, (o) for maintenance
Lanza 1997 USA Multicenter	***Recurrence:*** *12 months:* (ITT) 62% (pl) 27%(l) (Endo) 61% (pl), 26% (l) ***Symptoms:*** Median time to becoming symptomatic >12 months both groups *Asymptomatic during 9-12 months:* 75% (l), 58% (pl) *Antacid use (tabs/day):* median 0.08 (l), 0.23 (pl) (P<0.05)	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair	
Kovacs 1999 USA Multicenter	***Recurrence:*** *1 month:* 27% (pl), 13% (l15), 6% (l30) *12 months:* 30% (l15), 15% (l30) All patients on (pl) experienced recurrence or withdrew from study by 6 months. ***Symptoms:*** *Symptom free at* *12 months:* 82% (l15), 76% (l30) All patients on (pl) experienced symptoms, recurrence or withdrew from study by 6 months *Antacid use:* median use (tabs/day): 0.21 (pl), 0 (l15), 0.01 (l30) NS	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Withdrawals due to adverse events: 2 (pl), 3 (l15), 1 (l30).No significant changes from baseline on labs, physical exam, or ECG. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug. Changes in Grimelius-positive	Fair	Prior to enrollment, healing was achieved in all patients with (l30).

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Russo 1997 Italy Multicenter	Mean age 44 68% male 55% smokers (43% >15/day) 32% alcohol users H. pylori positive: 91%	If (l30) during healing trial: lansoprazole 15 mg or placebo once daily x 12 months or until recurrence	If (r) during healing trial: ranitidine or placebo 150mg once daily x 12 months or recurrence	Healing: 132 enrolled ((68 (l), 64 (ran) Maintenance: 108 enrolled (30 (l30/l15), 28 (l30/pl), 24 (ran/ran), 26 (ran/pl)
Graham 1992 USA Multicenter	Mean age 48 (o), 50 (ran), 47 (pl) % male: 75% (o), 67% (ran), 69% (pl) Mean index ulcer size (cm): 0.9 (o), 0.8 (ran) (P<0.01); (pl) not reported other variables reported as NS	None	None	240 enrolled (80% of (o), 63% of (ran) and 27% of (pl) patients eligible enrolled)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Russo 1997 Italy Multicenter	***Recurrence:*** (ITT) *3 months:* 7% (l/l), 14% (l/pl), 8% (ran/ran), 27% (ran/pl) *6 months:* 17% (l/l), 32% (l/pl), 33% (ran/ran), 46% (ran/pl) *9 months:* 23% (l/l), 36% (l/pl), 38% (ran/ran), 50% (ran/pl) *12 months:* 23% (l/l), 39% (l/pl), 46% (ran/ran), 50% (r/P) (P=0.081 (l/l) vs (ran/ran) ***Symptoms:*** results not reported	***Maintenance*** : Reported as 3% (l/l), 18% (l/pl), 0% (ran/ran) (ran/pl) not reported	*Healing:* Good/Fair *Maintenance:* Fair/Poor	Healing: (l30) or (ran). baseline information on maintenance phase participants not reported. Attrition/compliance for maintenance not reported. Results for symptoms during healing phase not reported.
Graham 1992 USA Multicenter	Life table analysis relapse rates: 78% (o), 60% (ran), 50% (pl) (NS)	None reported	Fair	Followup study of (o20) vs (ran) or (o20) vs (pl)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	Mean age 55 57% male 52% smokers 57% H. Pylori positive 24% antacid use 96% had >/= 0.5cm ulcer	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 6 weeks based on outcome measure timing.	20 mg of omeprazole	227 enrolled	***Healing rates by ITT:*** *3 weeks:* 58% (r), 61% (o) *6 weeks:* 91% (r and o) *3 weeks:* 58% (r), 63% (o) *6 weeks:* 93% (r and o) *3 weeks:* 60% (r), 59% (o) *6 weeks:* 52% (r), 44% (o) ***Pain severity:*** no pain *3 weeks:* 68% (r), 61% (o) *6 weeks:* 84% (r), 68% (o) Overall well-being at 3 and 6 weeks comparable for both groups
DiMario 1994 Italy Multicenter Maintenance study	Mean age 47.9 (23-75) 71% male 13% gastric ulcers, 79% duodenal ulcers, 8% both gastric and duodenal ulcer All ulcers resistant to H2 blocker therapy (unhealed after 8 weeks of therapy)	Omeprazole 20 or 40 mg daily for 4 weeks, extended to 8 weeks if necessary. After healing: omeprazole 20 mg daily (30 patients) omeprazole 20 mg every other day (29 patients) omeprazole 20 mg twice weekly (29 patients)	ranitidine 150 mg (12 patients only)	# screened, eligible not reported, 102 enrolled	***Recurrence (6 months) by ITT:*** 23.3% Omeprazole 20 mg daily (p <0.02 vs ranitidine) 19.4% Omeprazole 20 mg every other day (p<0.005 vs ranitidine) 58.6% Omeprazole 20 mg twice weekly 66.7% Ranitidine 150 mg

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r)and 10.0 pg/ml (o).	Fair	
DiMario 1994 Italy Multicenter Maintenance study	No side effects were reported during the maintenance treatment period; 1 patient reported headache in healing period (at oemp 40 mg daily; resolved). 11 patients dropped out (27% in omep 20 mg every day group, 0 in omep every other day, 73% in omep 20 mg twice weekly)	Poor-open, differential loss to followup.	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Kovacs 1999 USA Multicenter Maintenance Study	Mean age 58 (pl), 57 (l15), 58 (l30) 85% male 67% smokers 47% alcohol users 96% acute disease H-2 RA resistant	Lansoprazole 15 or 30mg once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	Placebo once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	52 patients eligible, 49 enrolled	***Recurrence:*** median < 2 months (pl), > 12 months (l groups) *At 1 month:* 40% (pl), 0% (l15), 7% (l30) *12 months:* 0% (pl), 17% (l15), 7% (l30) (P<0.001 (l groups vs (pl)) ***Symptoms:*** Of those asymptomatic at baseline 0%? (pl), 100% (l15), 59% (l30) no symptoms at 12 months *Antacid use:* (tabs/day) Median 0.38 (pl), 0.02 (l15), 0.01 (l30)
Cooperative Study 1990 UK Multicenter	Mean age: 57 (o), 61 (ran) 54% male 65% smokers 74% alcohol users	Omeprazole 40mg once daily x 2 to 8 weeks	Ranitidine 150mg twice daily x 2 to 8 weeks	46 enrolled (21 (o), 25 (ran)) 27 enrolled in followup study (12 (o), 15 (ran))	***Healing (PP):*** *4 weeks:* 81% (o), 58% (ran)(NS) *8 weeks:* 93% (o), 87% (ran)(NS) ***Pain free (baseline not reported)*** *2 weeks:* 53% (o), 42% (ran)(NS) *4 weeks:* 73% (o), 38% (ran)(NS) *8 weeks:* 50% (o), 44% (ran) (NS) Nighttime pain at 2 weeks (o) < (r), data not reported, (P<0.03) Daytime pain (o) < (ran)in weeks 3 and 4 by diary card, data not reported, (P<0.03) ***Recurrence:*** *6 months:* 42% (o), 67% (ran)(NS)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Kovacs 1999 USA Multicenter Maintenance Study	39 patients reported 1 or > adverse events reported (13 (pl), 14 (l15), 12 (l30), NS. The most common adverse events that were possibly or probably related to study drug were diarrhea (0%(pl), 0% (l15), 13.3% (l30) and constipation (12.5% (pl), 5.3% (l15), 0% (l30)). 7 patients withdrew due to adverse events (4 (pl), 1 (l15), 2 (l30)). No clinically significant lab changes, vital signs, or ECG seen. Serum Gastrin Significantly (P</= 0.003) greater changes from baseline seen in (l) groups vs (pl) 4 (l15), and 15 (l30) fasting levels > 200 pg/ml during study Increases occurred within 1 month of starting (l) and returned to baseline within 1 month of stopping drug Gastric Mucosal Biopsy Increases in Grimelius positive cell density in the corpus (from baseline) 121 cells/mm2 (pl), 146 cells/mm2 (l15), 176 cells/mm2 (l30) (P=0.001 vs (pl)). No other cell changes seen.	Fair	
Cooperative Study 1990 UK Multicenter	1 death judged to be unrelated to study. 9 patients reported adverse events (5 (o), 4 (ran)). The most common were GI symptoms.	Poor	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	Mean age 55 (o20), 57 (o40), 58 (ran) % smokers 61% (o20), 60% (o40), 56% (ran) % alcohol users 60% (o20), 57% (o40), 50% (ran) NSAID use 11% (o20), 12% (o40), 11% (ran)	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	602 enrolled (436 gastric ulcers, 166 prepyloric ulcers)	***Healing:*** ***Gastric + prepyloric (PP analysis):*** *4 weeks:* 69% (o20), 80% (o40), 59% (ran) *8 weeks:* 89% (o20), 96% (o40), 85% (ran) ***ITT analysis reported as 'similar'*** *Prepyloric only:* (PP analysis) *2 weeks:* 33% (o20), 42% (o40), 27% (ran)(NS) ***NSAID users (PP analysis)*** *4 weeks:* 61% (o20), 81% (o40), 32% (ran) *8 weeks:* 82% (o20), 95% (o40), 53% (ran) ***Symptoms:*** *None at 2 weeks:* 62% (o20), 69% (o20), 55% (ran)((o40) vs (ran)P= 0.02) *Followup Study:* *Healing maintained at 6 months:* 59% (O40 and O20), 53% (ran) (P=0.03 (o40) vs (ran)) *No symptoms 'during followup':* 52% (O40 and O20), 48% (ran)(P=0.02 (o40) vs (ran))
Rossini 1989 Italy Single center	Data not reported – stated to be similar	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	18 enrolled (number per group not stated)	***Healing*** *4 weeks:* 78% (o), 50% (ran) *8 weeks:* 100% (o), 87% (ran) Pain disappeared almost completely in both groups by two weeks
Classen 1985 Germany Multicenter	Data not reported – stated to be similar	Omeprazole 20mg once daily x 4 to 6 weeks	Ranitidine 150mg twice daily x 4 to 6 weeks	184 enrolled	***Healing (PP analysis only):*** *2 weeks:* 43% (o), 45% (ran) (NS) *4 weeks:* 81% (o), 80% (ran) (NS) *6 weeks:* 95% (o), 90% (ran) NS ***Symtoms:*** "equally good with either drug"

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	106 patients reported adverse events (34 (o20), 32 (o40), 40 (ran)). The most common were GI symptoms, similar in all groups. Numbers withdrawn or lost to follow up: 21 (o20), 19 (o40), 22 (ran) 3 patients died during study (all on (o40)) of causes shown to be unrelated to study drug, 2 patients withdrawn due to abnormal labs also shown to be unrelated to study drugs ((1 (o40), 1 (ran)).	Good/Fair	Patients enrolled in followup study not well described, attrition not described.
Rossini 1989 Italy Single center	None reported in either group	Fair/poor	
Classen 1985 Germany Multicenter	Not reported	Poor	This appears to be a report in English of two trials previously published in German, therefore the quality of the trials may be higher than appears from this paper.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Bardhan 1994 United Kingdom and Sweden Multicenter	Mean ages 60 (l60), 59(l30), 57(r) 57% males 65% UK 35% Sweden 52% smokers 60% alcohol use 11% NSAID use	Lansoprazole 30mg or 60mg once a day x 4 to 8 weeks	Ranitidine 300mg every night x 4 to 8 weeks	250 enrolled	***Healing rates:*** *4 weeks:* *of those with endoscopy:* 78% (120), 84% (160), 61% (ran) ***ITT:*** 72% (l30), 73% (l60), 52% (ran) ***PP:*** 80% (l30), 78% (l60) 57% (ran) *8 weeks:* *of those w/endoscopy:* 99% (l30), 97% (l60), 91% (ran) ***ITT:*** not reported ***PP:*** 98% (l30), 100% (l60), 90% (ran) *Symptoms:* proportaion symtom free at 4 weeks: *Pain:* 75% (l30), 72% (l60), 65% (ran) *Nausea:* 88% (l30), 89% (l60), 76% (ran) *Vomiting:* 100% (l30), 87% (l60), 89% (ran)
Michel 1994 France Multicenter	Mean age 52 (l), 56 (ran) 69% male 38% smokers 52% alcohol users 42% NSAID users mean ulcer size 12mm (l), 11mm (ran)	Lansoprazole 30mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	158 enrolled	***Healing:*** *4 weeks:* ITT 68% (l), 56% (ran)NS PP: 80% (l), 62% (ran)(p<0.05) *8 weeks:* ITT 81% (l), 76% (ran)(NS) PP: 100% (l), 87% (ran)(P<0.05) *No epigastric pain:* (at baseline 26% (l), 22% (ran)) *4 weeks:* 73% (l), 72% (ran)(NS) *8 weeks:* 95% (l), 92% (ran)(NS)
Capurso 1995 Italy Multicenter	Data not reported – stated to be similar	Lansoprazole 30mg once daily x 2 to 8 weeks	Ranitidine 300mg once daily x 1 x 2 to 8 weeks	74 enrolled (34 (l), 35 (o), 5 not reported)	***Healing rates:*** *2 weeks:* 41.4% (l), 26.5% (ran) *4 weeks:* 79.3% (l), 61.8% (ran) *8 weeks:* 96.6% (l), 94.1% (ran) ***Pain:*** at 2 weeks no significant difference between groups 64% pain free

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Bardhan 1994 United Kingdom and Sweden Multicenter	69 patients experienced 91 adverse events, 26% (l30), 27% (l60), 30% (ran). The most common thought to be possibly or probably related to study drug were diarrhea and headache.	Fair	
Michel 1994 France Multicenter	38 patients reported adverse events. 4 withdrawn due to serious adverse events all (r)group). 3 of these were deaths (1 acute heart failure, 2 acute respiratory distress), the forth withdrawn due to femur fracture resulting from hypotension. GI symptoms (diarrhea, constipation were the most common adverse effects reported in both groups.	Fair	Numbers of subjects in PP analysis do not add up. Table 2 shows 3 patients withdrawn due to adverse events, but text reports 4. Table 2 reports 16 lost from (l) (79 - 16 = 63) but only 62 included in PP analysis. Likewise, number analyzed at 4 weeks on (ran)reported as 68, but 12 reported lost (79 - 12 = 67)
Capurso 1995 Italy Multicenter	8 adverse effects reported: 3 (ran), 3 (l), and 2 (o) No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Hotz 1995 Germany Multicenter (28)	Median age 55 (p), 57 (r) 60% male 45% smokers 9.7% everyday alcohol users mean ulcer diameter 10.9 (p), 11.2 (r)	Pantoprazole 40mg once daily x 2, 4 or 8 weeks depending on healing. (2:1 randomization p:r)	Ranitidine 300mg every night x 2, 4 or 8 weeks depending on healing	248 enrolled.	***Healing:*** *2 weeks:* ITT: 33% (p), 17% (ran) (P<0.01) PP: 37% (p), 19% (ran) (P<0.01) *4 weeks:* ITT 77% (p), 52% (ran) (P<0.001) PP: 87% (p), 57% (ran) (P<0.001) *8 weeks:* ITT 86% (p), 72% (ran) (P<0.01) PP: 97% (p), 80% (ran) (P<0.001) No pain:(13% (p), 8% (ran) at baseline) (PP) *2 weeks: 7*2% (p), 68% (ran) (NS) Based on diary card, no difference between groups in time to becoming pain free Other GI symptoms also improved in both groups.
Tsuji 1995	Mean age 64 81% male 50% H. pylori positive	Lansoprazole 30mg once x 4 to 8 weeks	Famotidine 40mg x 4 to 8 weeks		***Healing:*** *4 weeks:* 71% (l), 29% (f) *8 weeks:* 83% (l), 57% (f) Symptoms not reported
Okai 1995	Mean age 54 (range 36-86) (l30) 59 (range 39-80) (f) 75% male 71% smokers 38% ulcer size >15mm	Lansoprazole 30mg once daily x 2 to 8 weeks	Famotidine 40mg once daily x 2 to 8 weeks		***Healing:*** *4 weeks:* 50% (l), 0% (f) *8 weeks:* 54.5% (l), 18.2% (f) (from Kovacs, 1998) **Symptoms:** Pain free at week 1:80% (l), 60% f) (NS)
Bate 1989 UK and Republic of Ireland Multicenter	Mean age 57 47% male 59% smokers 3% ulcer size >10mm	Omeprazole 20mg once daily x 4 to 8 weeks	Cimetidine 800mg x 4 to 8 weeks	197 enrolled (105 (o), 92 (c))	***Healing (ITT):*** *4 weeks:* 73% (o), 58% (c) (P<0.05) *8 weeks:* 84% (o), 75 (c) (NS) ***Symptoms*** ***Pain free*** *4 weeks:* 81% (o), 60% (c) (P<0.01) *8 weeks:* "difference no longer significant" *4 weeks* (but not at 8 weeks) Daytime pain and heartburn less in (o) (P<0.05) data not reported. No difference in nocturnal pain or nausea Diary cards: 2 weeks: (o) better than (c) for daytime pain (P<0.01), nighttime pain (P<0.05) and antacid use (P<0.0001)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Hotz 1995 Germany Multicenter (28)	26 patients reported adverse events (15 (p), 11 (ran). The most frequent was diarrhea (3) and headache (2) on (pl), and sleep disorder (2) on (ran). 4 (p) and 3 (ran) withdrew due to adverse events, 1 (r) patient had elevated serum transaminase levels, otherwise lab values were normal. Median change in serum gastrin levels at 8 weeks: 30pg.ml (pl), 12pg/ml (ran), median values at all time points were higher in the (p) group.	Good/Fair	
Tsuji 1995	None	Fair	
Okai 1995	None	Fair	
Bate 1989 UK and Republic of Ireland Multicenter	32 patients reported adverse events (19% (o), 15% (c)). 2 were serious, but considered unrelated to study. 7 (4 (o),3 (c)) withdrew due to adverse events (2 in (o) were due to lack of efficacy). The most common adverse events were GI and CNS system related in both groups	Fair/Poor	

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Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Lauritsen 1988 Denmark Multicenter	Mean age 57 45% male 74% smokers mean ulcer 9.7, 10.7 mm	Omeprazole 30mg once daily x 6 weeks	Cimetidine 1000mg x 6 weeks	179 eligible, 176 enrolled (3 chose not to participate)	***Healing:*** *2 weeks:* ITT: 54% (o), 39% (c) PP: 55% (o), 42% (c) *4 weeks:* ITT 81% (o), 73% (c) PP: 85% (o), 77% (c) *6 weeks:* ITT 86% (o), 78% (c) PP: 89% (o), 86% (c) ***No pain:*** (24% (o), 14% (c) at baseline) *2 weeks:* 48% (o), 29% (c) *4 weeks:* 57% (o), 47% (c) *6 weeks:* 62% (o), 58% (c) Number of hours of pain at 6 weeks: 7.5 (o), 10.5 (c)
Danish Omeprazole Study Group 1989	Median age 60 (range 52-71) (o) 61 (range 50-72) (c) 48% male 69% smokers	Omeprazole 30mg x 2 to 6 weeks	Cimetidine 1000mg x 2 to 6 weeks	161 enrolled 146 evaluated	***Healing:*** *2 weeks:* 41% (o), 41% (c) *4 weeks:* 77% (o), 58% (c) *6 weeks:* 88% (o), 82% (c) ***Symptoms*** ***Mean days with pain:*** *2 weeks:* 5 (o), 5.5 (c) *4 weeks:* 4.3 (o), 3.8(c) *6 weeks:* 2.4 (o), 2.4(c) (all NS) 6-month followup (untreated) no difference in relapse rate (Endo):17% (o), 19% (c)
Aoyama 1995	Data not reported – stated to be similar	Lansoprazole 30mg x 2 to 8 weeks	Cimetidine 800mg x 2 to 8 weeks	107 enrolled 84 evaluated	***Healing:*** *2 weeks: 14% (l), 6% (c)* *4 weeks:71% (l), 47% (c)* *6 weeks:* 94% (l), 75% (c)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
Lauritsen 1988 Denmark Multicenter	12 reports of adverse events. (o): one each: headache, fatigue, transient diarrhea, gastroenteritis, muscle pain. (c): one each of headache, dry mouth, 2 each of dizziness, impotence	Fair	
Danish Omeprazole Study Group 1989	3 withdrawals due to adverse effects in (c) group due to 'other diseases' and urticarial reaction. 19 other adverse events reported. (o) group: allergic edema, itching, diarrhea (2 cases), tremor, polyuria, shoulder pain, and pulmonary edema.. (c) group: itching, diarrhea, constipation (2), dizziness (2), fatigue (2), insomnia, and back pain (2).	Poor	
Aoyama 1995	Nor reported.	Poor	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/Eligible/ Enrolled
Hawkey 1998 International (14 countries including USA) Treatment or prevention	Mean age 58 (range 20 to 85) 38% male 23% smokers 39% H. pylori positive 8% history of bleeding ulcer 41% gastric ulcer 38% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily (duration not clearly stated, assumed to be 8 weeks)	200 mcg of misoprostol four times daily	935 enrolled
Yeomans 1998 International (15 countries) Traetment or prevention	Mean age 57 33% male 10% history of bleeding ulcer 39% gastric ulcer 46% H. pylori positive 44% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily for four or eight weeks	150 mg of ranitidine twice daily for four or eight weeks	541 enrolled

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
Hawkey 1998 International (14 countries including USA) Treatment or prevention	***Treatment Success at 8 weeks:*** 76% (o20), 75% (o40), 71% (m) (NS) ***ITT analysis:*** 75% (o20), 75% (40), 71% (m) ***GU only:*** 87% (o20), 80% (o40), 73% (m) (P=0.004 (o20) vs (m); 0.14 (o40) vs (m) ***GU and DU:*** 85% (o20), 79% (o40), 74% (m) ***DU only:*** 93% (o20), 89% (o40), 77% (m) ***Erosions only:*** 77% (o20), 79% (o40), 87% (m) ***H. pylori positive:*** 83% (o20), 83% (o40), 69% (m) ***H. pylori negative:*** 73% (o20), 70% (o40), 74% (m) ***Symptoms:*** Reduction in mod-severe dyspepsia at 4 weeks 34% (o20), 39% (o40), 27% (m) Proportion of days with abdominal pain 43% (o20), 43% (o40), 50% (m) Proportion of days with heartburn 16% (o20), 14% (o40), 29% (m) QOL (completed by 68% (o20), 66% (o40), 62% (m)) Gastrointestinal Symptom Rating Scale at 8 weeks change in total score-0.47 (o20), -0.36 (o40), -0.20 (m) change in reflux score: -0.82 (o20), -0.75 (o40), -0.33(m) change in diarrhea score: -0.24 (o20), -0.06 (o40), +0.22 (m) Nottingham Health Profile change in sleep score: -3.1 (o20), -8.6 (m), (o40 not reported)	470 patients reported adverse events (48% (o20), 46% (o40), 59% (m) Most common reported was diarrhea (4.5% (o20), 5.3% (o40), 11.4 % (m)	Fair	Patients without healing at eight weeks received open treatment with 40 mg of omeprazole daily for a further four to eight weeks.
Yeomans 1998 International (15 countries) Traetment or prevention	***Treatment Success at 8 weeks:*** 80% (o20), 79% (o40), 63% (ran) ***GU only:*** 84% (o20), 87% (o40), 64% (ran) ***DU only:*** 92% (o20), 88% (o40), 81 (ran) ***Erosions only:*** 89% (o20), 86% (o40), 77% (ran) ***H. pylori positive*** *:* 83% (o20), 82% (o40), 72% (m) *H. pylori negative:* 75% (o20), 71% (o40), 55% (m) ***Symptoms:*** *reduction of 'moderate to severe' category at 4 weeks:* 46% (o20), 38% (ran) (o40 not reported)	190 moderate to severe adverse events were reported (30% (o20), 38% (o40), 40% (r) GI effects (diarrhea, nausea, constipation, and flatulence) were the most common reported Discontinuation of therapy due to either and adverse event or lack of efficacy (not reported separately): 2.8% (o20), 3.2% (o40), 8.5% (ran)	Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/Eligible/ Enrolled
Agrawal 2000 USA and Canada, multicenter (43 centers_ healing only	Mean age 60 35% male 90% white 21% smokers 31% alcohol users 29% H. pylori positive	Lansoprazole, 15 or 30 mg once daily for 8 weeks	Ranitidine 150 mg twice daily for 8 weeks	Endoscopy was performed on 669 patients, 353 met inclusion criteria.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
Agrawal 2000 USA and Canada, multicenter (43 centers_ healing only	***Healing: Gastric Ulcer*** *4 weeks:* 47% (l15), 57% (l30), 30% (ran) *8 weeks:* 69% (l15), 73% (l30), 53% (ran) ***GU and DU 8 weeks** :* 93% (l15), 81% (l30), 88% (ran) ***GU or erosions 8 weeks:*** 85% (l15), 100% (l30), 86% (l30) ***H. pylori positive: 8 weeks:*** 67% (l15), 82% (l30), 60% (ran) ***H. pylori negative** :* 70% (l15), 69% (l30), 51% (ran) ***Symptoms:*** *4 weeks:* no daytime pain 66% (l15), 64% (l30), 60% (ran) no nighttime pain 67% (l15), 69% (l30), 64% (ran) % days antacids used 67% (l15), 70% (l30), 62% (ran) *8 weeks:* no daytime pain 70% (l15), 66% (l30), 63% (ran) no nighttime pain 71% (l15), 71% (l30), 69% (ran) % days antacids used 69% (l15), 71% (l30), 64% (ran)	33 patients reported an adverse event, 15 patients stopped taking study medication because of adverse events (5 (l15), 4 (l30), 6 (ran)). The most commonly reported treatment-related event was diarrhea.	Good/Fair	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control	Other Medications
Lai et al. 2002	123 patients, double blind, ITT. Hong Kong, mean age 70 (range 18-80), female 28%, race NR. 245 screened, 171 eligible by H. pylori, 127 treated, 4 H. pylori uneradicated.	History of cerebrovascular accident (52%) or heart disease (48%) - endo revealed gatric (74%), duodenal (21%) or gastroduodenal (5%) ulcer.	- History of stroke or ischemic heart isease requiring long-term aspirin therapy; - Ulcer developed after at least one month low-dose aspirin therapy; - H. pylori infection; - Ulcer and H. pylori successfully eradicated during initial healing phase of study; - No esophagitis, history of ulcer surgery, comcomitant treatment with NSAIDs, corticosteroids or anticoagulant agents, active cancer, or allergic to study drugs.	30 mg (l) + 100 mg aspirin bid for median 12 months	Matching placebo + 100 mg aspirin bid	Antacid permitted, advised to avoid other NSAIDs if possible
Graham, 2002	US and Canada Multicenter Mean age 60 65% female 90% white, 6% black, 4% other.	No H. pylori; reason for long-term NSAID use not reported, previous GI disease: 59% reflux esophagitis, 50% duodenal ulcer, 99% gastric ulcer.	Age 18 or older, h/o endoscopically-documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding, and treatment with stable, full therapeutic doses of an NSAID (except nabumetone or aspirin >1300 mg/day) for at least the previous month.	Lansoprazole 15 or 30 mg for 12 weeks	Misoprostol 200 mcg qid for 12 weeks	40% ibuprofen, 35% naproxen, 32% diclofenac, 22% aspirin or aspirin combinations, 17% piroxicam, 34% other NSAIDS

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times aday Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (continued)

Author Year	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Chuen et al. 2002	Primary endpoint: recurrence of ulcer complications (bleeding, outlet obstruction, perforation). Secondary endpoint: recurrence of ulcer.	Clinical Bleeding: (l) = 0, (pl) = 8 (p≤.01) Ulcer recurrence: (l) = 1, (pl) = 9 (p=.008) H. pylori recurrence: (l) = 0, (pl) = 4 (p≤.05)	Death: (l) = 1, (pl) = 0 Other adverse effects NR.	
Graham 2002	Occurrence of gastric ulcer (definition of gastric ulcer not specified), included analysis with withdrawals considered treatment failures (having a gastric ulcer).	***Treatment success:*** *Free of gastric ulcer by week 12 (per protocol):* *(pl)* :51% (m): 93% (l15): 80% (l30): 82% ***Treatment success:*** *Results when withdrawals classified as treatment failures:* *(pl)* :34% (m): 67% (l15): 69% (l30): 68%	Withdrawals due to adverse events: (pl) 6.7%, (m) 10.4%, (l15) 2.9%, (l30) 7.5%; Higher percentage of treatment related adverse events in misoprostol group (31% (m), 10% (pl), 7% (l15), 16% in (l30); most common diarrhea. One upper GI tract hemorrhage (l15).	Fair: randomization and allocation method not reported.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (m) misoprostol (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (continued)

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control	Other Medications
Bianchi Porro 2000	Italy Single center Mean age 59.9 (range 22-80) 83% female ethnicity not given	63% rheumatoid arthritis 38% osteoarthritis.	Over age 18, with rheumatoid arthritis or osteoarthritis, treated with effective and constant doses of NSAIDs (diclofenac, ketoprofen, indomethacin) for at least 8 weeks prior to start of study. Lanza endoscopic grade 0,1, or 2.	Pantoprazole 40 mg	Placebo	37% diclofenac, 34% ketoprofen, 35% indomethacin.
Labenz et al. 2002	2264 patients screened, 832 randomized, 660 analyzed - in 3 countries in central Europe, double blind, not ITT. Mean age: 55 Male: 38%	Systemic inflammatory disease (24%), noninflammatory disease (73%), mild dyspepsia (42%), Lanza score "0" on study entry (stomach 68%; duodenum 89%).	Age >18 years with inflammatory disease of musculoskeletal system requiring NSAID treatment ≥5 weeks, and H. pylori positive. Excluded for ulcer or history of ulcer, clotting disorders, prior regular use of NSAIDS (except aspirin ≤100 mg/day), antibiotics, PPIs, misoprosol, or bismuth salts within 4 weeks; regular use of H2R antagonists, prokinetics or sucralfate; systemic corticosteroids, known or suspected intolerance to study drug, severe concomitant diseases; previous gastric surgery; pregnancy or nursing; and dyspepsia therapy.	OAC-O = omeprazole 40 mg + amoxicillin 2 g +clarithro-mycin 1000 mg for 1 week, then 20 mg ome for 4 weeks. O-O = 20 mg ome for 5 weeks.	OAC-P = OAC for 1 week, then placebo for 4 weeks. P-P = placebo for 5 weeks.	NSAID treatment: diclofenac 100-150 mg, and could add tramadol 200 mg. Dyspeptic therapy with an antacid.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times aday Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (continued)

Author Year	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Bianchi Porro 2000	Occurrence of gastric or duodenal ulcers (grade 4, Lanza classification) after 4 and 12 weeks, or patients who discontinued the study due to lack of efficacy leading to discontinuation of the study medication, an adverse event which was assessed by the study investigator as possibly or definitely related to the study medication.	***Ulcer status assigned (treatment failure):*** (p)*:* 13 with endoscopically-proven peptic ulcer, 3 due to lack of efficacy, 2 adverse events (pl)*:* 9 with endoscopically-proven peptic ulcer (1 with both gastric and duodenal ulcer), 1 lack of efficacy , 2 adverse events. ***Endoscopically proven duodenal and/or gastric ulcers:*** (p)*:* 13 (pl)*:* 9	4.3% (p) (m) unrelated to treatment, vomiting possitbly related, diarrhea definitely related), 5.9% (pl) (diarrhea possibly related, asthenia definitely related), all withdrew for adverse events.	Fair/Good: concealment of allocation not reported
Labenz et al. 2002	Primary endpoint: endoscopically proved peptic ulcer. Secondary endpoints: dyspeptic complaints, signs of gastrointestinal bleeding.	OAC-O vs. O-O vs. OAC-P vs. P-P Developed peptic ulcers - Total: 2/173 (1.2%) vs. 0/155 vs. 2/161 (1.2%) vs. 10/171 (5.8%) - Duodenal: 0/173 vs. 0/155 vs. 2/161(1.2%) vs. 7/171(4.1%) - Gastric: 2/173 (1.2%)vs. 0/155 vs. 0/161 vs. 3/171 (1.8%) (Bonferroni p-value significant for all ome groups vs. pla) Dyspepsia developed requiring therapy: 10.4% vs. 12.3% vs. 10.6% vs. 19.9% (All treatment groups significantly different from pla only group - p-value NR)) Negative H. pylori status: 85.3% vs. 21.9% vs. 81.3% vs. 11.8%	201 of 660 patients reported 302 adverse events (no details reported): OAC-O 31% O-O 16% OAC-P 26% P-P 26% Diarrhea more frequent in antibiotic groups: OAC-O 8.8% O-O 3.0% OAC-P 8.4% P-P 3.3%	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (m) misoprostol (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control	Other Medications
Hawkey, 1998	93 centers in 14 countries mean age 58 (range 20-85) 64% female ethnicity not given	38% rheumatoid arthritis, 47% osteoarthritis, 13% other, 2% combinations.39 % gastric ulcer with or without erosions, 20% duodenal ulcer with or without erosions, 4% gastric and duodenal ulcer with or without erosions, 36% erosions only.	Patients who successfully healed during treatment phase of study. Age 18 to 85, with any condition requiring continuous treatment with oral or rectal NSAIDS above a predetermined minimal dose (no maximal dose). Minimal (and mean) daily oral doses: 50 mg (129 mg) diclofenac, 100 mg (137 mg) ketoprofen, 500 mg (844 mg) naproxen. By endoscopy, any or all of the following: ulcer, defined as a mucosal break at least 3 mm in diameter with definite depth in the stomach, duodenum, or both, more than 10 gastric erosions, and more than 10 duodenal erosions.	Omeprazole 20 mg	Misoprostol 200 mcg bid or placebo	At baseline (all patients):most common diclofenac (23%), naproxen (22%), ketoprofen (16%).
Yeomans 1998	73 centers in 15 countries; mean age 56 (range 20-80); 69% female; ethnicity not given	44% rheumatoid arthritis, 32% osteoarthritis, 6% psoriatic arthritis, 5% anklyosing spondylitis,	Age 18 to 85, with any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximal dose),and not more than 10 mg prednisolone or equivalent per day. By endoscopy, any or all of the following: ulcers 3 mm of more in diameter, more than 10 erosions in stomach, more than 10 erosions in the duodenum. (Lanza scale)	Omeprazole 20 mg	Ranitidine 150 mg bid	Not reported for maintenance phase. Most common at baseline (including healing phase) diclofenac (29%), indomethacin (23%), naproxen (16%)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Hawkey, 1998	Development of any of the following: an ulcer, more than 10 gastric erosions, more than 10 duodenal erosions, at least moderate symptoms of dyspepsia, or adverse events resulting in the discontinuation of treatment.	***In remission at 6 months:*** ***(***o20):61%(m): 48%(pl): 27%p = 0.001 for (o20) vs (m) *Gastric ulcers at relapse:(* o20):13%(m):10%(pl):32% *Duodenal ulcers at relapse:(* o20): 3%(m):10%(pl):12%	Withdrawals due to adverse events: (o20): 3.9%, (m): 7.7%, (pl): 1.9%; most common diarrhea (7.6% (o20), 8.4% (m), 4.5% (pl), abdominal pain (5.1% (o20), 4.7% (m), 5.8% (pl). One perforated duodenal ulcer after 31 days of (pl).	Fair: randomization and allocation method not reported, not intention-to-treat.
Yeomans 1998	Remission defined as absence of a relapse of lesions, dyspeptic symptoms, and adverse events leading to the discontinuation of treatment.	***In remission at 6 months:*** **(**o20): 72%(r): 59%p = 0.004	Any adverse event: (o20): 64%, (r): 58%; withdrawals due to adverse events: 6.1% (o20), 3.2% (ran). Most common arthritis, rheumatoid arthritis, vomiting (2.9% (o20), 2.3% (ran)), abdominal pain (2.9% (o)o, 1.9% (ran)), diarrhea (3.3% (o20), 1.4% (ran)). One bleeding duodenal ulcer after 10 days of (o20).	Fair: randomization and allocation method not reported, not intention-to-treat.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 9. Adverse effects in short term RCTs: PPI versus PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Castell 1996 US Multicenter	GERD	Lansoprazole 15 mg or 30 mg	Omeprazole 20 mg	1070	(o20): 2% (l30): 1.7% (l15): 0.9%
Johnson et al. 2002 UK & Ireland Multicenter, crossover	Chronic PPI treatment for benign ulcers or GERD	4 weeks (o) 20 mg/day	4 weeks (r) 20 mg/day	240	30/240 (12.5%)
Hatlebakk 1993 Norway/ Sweden Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 20 mg	229	(o20): 0.9%(l30):0
Mee 1996 UK and Ireland Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 20 mg	604	Not reported
Mulder 1996 Netherlands Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 40 mg	211	None
Dekkers 1999 European Multicenter	GERD	Rabeprazole 20 mg	Omeprazole 20 mg	202	(r20): 1% (o20): 0
Delchier 2000 European Multicenter	GERD	Rabeprazole 20 mg or Ransoprazole 10 mg	Omeprazole 20 mg	300	(r10): 5% (r20): 5% (o20): 2%

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Castell 1996 US Multicenter	Any adverse event:(l15) 44.5%, (l30) 55.7%, (o20) 53.4%. Most commonly reported events headache, diarrhea, nausea. More patients in (ll5) reported nausea (p<0.05). 6 severe events possibly or probably related to medication (4 in (o20) , 1 in (l15), 1 in (l30).	Fair
Johnson et al. 2002 UK & Ireland Multicenter, crossover	(o) = 115 (51%) reported 114 mild, 117 moderate, and 30 serious treatment-emergent AEs. (r) = 120 (52.6%) reported 97 mild, 118 moderate, and 28 severe treatment-emergent AEs. No significant differences in AEs between groups. No difference in general preference for (o) or (r). - More patients prefer (r) for "absence of side effects" (p=.047), among those with any preference (46%). - More patients prefer (r) for "unexpected positive side effects" (p=.019), among those with any preference (28%). - More patients prefer tablet form of (r) as "easy to swallow" (p=.0001), among those with any preference (52%). - More patients prefer capsule form of (o) as "easy to pick up and hold" (p=.0003), among those with any preference (47%).	
Hatlebakk 1993 Norway/ Sweden Multicenter	32.8% (l30), 29.2% (o20) reported adverse event, One (o20) withdrawn for severe diarrhea. Headache in 4 pts (o20), none (l30).2 severe events (l30) (1 pharyngitis, 1 nausea, vomiting).	Poor
Mee 1996 UK and Ireland Multicenter	51% of all patients had at least one event, not broken down by treatment group. Most frequent events: headache (12% (l30), 11% (o20) diarrhea (9.4% (l30), 8% (o20) nausea (4.3% (l30), 4.7% (o20). 2 serious events (o20) (esophageal cancer (pre-existing) and vasovagal syncope and loose stools)	Good/Fair
Mulder 1996 Netherlands Multicenter	19% (l), 21% (o) No difference in change in gastrin levels between groups. No other events reported.	Fair
Dekkers 1999 European Multicenter	32% (r20) and 28% (o20) reported at least one adverse event. Headache, diarrhea, flatulence most common. Flatulence more common (o20) gr (4% vs 0%). One serious event (r20) (t wave changes).	Fair
Delchier 2000 European Multicenter	21% (r20), 26% (r10), and 23% (o20) reported at least one event. Abdominal pain, pharyngitis, bronchitis, headache, diarrhea most common. Four serious events, none related to medication. At week 4, incidences of elevated serum gastrin levels 16% (r20), 27% (r10), 20% (o20) (NS)	Fair

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Kahrilas 2000 US Multicenter	GERD	Esomeprazole 40 mg or 20 mg	Omeprazole 20 mg	1960	(e40): 2% (e20): 2.6% (o20): 2%
Richter 2001 US Multicenter	GERD	Esomeprazole 40 mg	Omeprazole 20 mg	2425	1% in each group
Corinaldesi 1995 European Multicenter	GERD	Pantoprazole 40 mg	Omeprazole 20 mg	241	(p40): 0.8% (o20): 1.7%
Dupas 2001 France Multicenter	GERD	Pantoprazole 40 mg	Lansoprazole 30 mg	461	(p40): 1.3% (l30): 2.5%
Dobrilla 1999 Italy Multicenter	Duodenal ulcer	Lansoprazole 30mg, then those with healed ulcer randomized to 15 or 30mg lansoprazole x 12 months	Omeprazole 40mg, then those with healed ulcer switched to omeprazole 20mg x 12 months	251 eligible (167 (l), 84 (o)) Maintenance phase: 243 enrolled (164 (l), 79(o))	Treatment:2.3 % (o), 9% (l)Maintenanc e:4% (l15), 2.8% (l30), 1.4% (o)
Chang 1995 Taiwan Single-center	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	83 enrolled (42 (l), 41 (o))	None reported.
Ekstrom 1995 Sweden Multicenter	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	279 enrolled (143 (l), 136 (o))	Not reported
Capruso 1995 Italy Multicenter	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	107 enrolled, (52 (l), 55(r))	Not reported.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Kahrilas 2000 US Multicenter	Total or per group not reported. Most common: headache 8.6% (e40), 8.7% (e20), 6.9% (o20) abdominal pain 3.7% (e40), 3.7% (e20), 4.2% (o20) diarrhea (4.6% (e40), 4.7% (e20), 3.9% (o20) flatulence (1.8% (e40), 3.5% (e20), 2.5% (o20) gastritis 2.5% (e40), 3.5% (e20), 2.5% (o20) nausea 3.8% (e40), 2.9% (e20), 3.1% (o20). No differences observed according to gender, age, or race. No serious drug-related events reported.	Fair
Richter 2001 US Multicenter	At least one adverse event reported in 32.2% in(e40), 34.3% in (o20). Most common: headache 6.2% (e40), 5.8% (o20) diarrhea 3.9% (e40), 4.7% (o20) nausea 3.0% (e40), 3.0% (o20) abdominal pain 2.6% (e40) 2.7% (o20) < 1% in each group had a serious event (0 considered treatment related)	Good
Corinaldesi 1995 European Multicenter	Adverse events reported by 15% of patients in (p40), 12% in (o20). Diarrhea, abdominal pain, hyperlipemia and constipation most frequently reported in (p40) , diarrhea most frequently (o20).	Fair
Dupas 2001 France Multicenter	Adverse events reported in 28% in p40 group, 17% in l30. Most common headache, diarrhea, elevation of hepatic enzymes, abdominal pain, skin disorders. 11 serious events (5 (p40) 6 (l30)).	
Dobrilla 1999 Italy Multicenter	16 during phase I (healing): 10 (6%, l), 6 (7.1%, o) 21 during Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o) Most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 (l15), 2 (l30), 3 (o))Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) had the least and the (l30) had the highest elevation at 6 and 12 months. At 6 months all values were returning to baseline.	Fair/Poor
Chang 1995 Taiwan Single-center	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication	Fair
Ekstrom 1995 Sweden Multicenter	68 adverse events occurred in 57 patients (23 (l), 34 (o)) (NS). A statistically significant difference was found in the mean change in ALT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o).	Fair
Capruso 1995 Italy Multicenter	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Chang 1995 Taiwan Single center	Duodenal ulcer	Lansoprazole 30mg once a day x 4 weeks	Omeprazole 20mg a day x 4 weeks	111 enrolled (57 (l), 54 (o)	Not stated in abstract
Fanti 2001 Italy Single center	Duodenal ulcer and H. pylori	Lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	Omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))	None
Dekkers 1999 European Multicenter	Duodenal ulcer	Rabeprazole 20mg	Omeprazole 20mg	205 enrolled (102 (r), 103 (o))	1.9% (o) 0% (r)
Dekkers 1998 European Multicenter	Gastric ulcer	Rabeprazole 20mg	Omeprazole 20 mg	227 enrolled	Not reported
Beker 1995 European Multicenter	Duodenal ulcer	Pantoprazole 40mg	Omeprazole 20mg	270 enrolled (135 each group)	0.74% (p)2.9% (o)
Lanza 1997 USA Multicenter	Duodenal ulcer maintenance	Lansoprazole 15mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled 88 (pl), 92 (l))	4.5% (pl) 2.2% (l)
Kovacs 1999 USA Multicenter	Duodenal ulcer maintenance	Lansoprazole 15 or 30mg once daily for up to 12 months	Placebo once daily for up to 12 months	56 enrolled19 (pl),18 (l15), 19 (l30)	21.5%(pl)17% (l15)5.3% (l30)
Russo 1997 Italy Multicenter	Duodenal ulcer maintenance	If (l30) during healing trial: Lansoprazole 15 mg or Placebo once daily x 12 months or until recurrence	If (r) during healing trial: Ranitidine or placebo 150mg once daily x 12 months or recurrence	108 enrolled 30 (l30/l15)28 (l30/p), 24 (ran/ran),26 (ran/p)	Not reported

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Chang 1995 Taiwan Single center	Hypergastrinemia with both agents. A few occurrences of reversible skin rash and constipation.	Not assessed
Fanti 2001 Italy Single center	"Mild and self-limiting" Total number not reported.1 (l) stomatitis and 1 (o) mild diarrhea	
Dekkers 1999 European Multicenter	43 patients reported at least one adverse event. (21 (r), 22 (o)). The most common was headache. 2 (o) withdrew due to adverse events (evaluated as unrelated to study)The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).	Fair
Dekkers 1998 European Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. No difference by sex, age, race.Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r) and 10.0 pg/ml (o).	Fair
Beker 1995 European Multicenter	21 patients reported adverse events (10, 7% (p), 11, 8% (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), GI hemorrhage and 4 (o), angina pectoris, hypertension, vertigo and abdominal pain. These patients were withdrawn from study. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair
Lanza 1997 USA Multicenter	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair
Kovacs 1999 USA Multicenter	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug.	Fair
Russo 1997 Italy Multicenter	Maintenance: 3% (l/l), 18% (l/pl), 0% (ran/ran). (ran/pl) not reported.	Fair/Poor

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Appendix A. Search Strategy

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1 Gastroesophageal reflux/ or "gerd".mp.
2 exp peptic ulcer/ or "peptic ulcer".mp.
3 1 or 2 (24054)
4 Proton pump/ai [Antagonists & Inhibitors]
5 proton pump inhibitor$.mp.
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp.
7 4 or 5 or 6
8 3 and 7
9 limit 8 to (human and english language)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial)
11 exp clinical trials/ or clinical trial$.mp.
12 exp epidemiologic research design/
13 observational stud$.mp.
14 11 or 12 or 13
15 9 and 14
16 10 or 15

Appendix B. Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan Oregon Health & Science University Evidence-based Practice Center

Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    Adequate approaches to sequence generation:
        Computer-generated random numbers
        Random numbers tables
    Inferior approaches to sequence generation:
        Use of alternation, case record numbers, birth dates or week days
    Not reported

2. Was the treatment allocation concealed?
    Adequate approaches to concealment of randomization:
        Centralized or pharmacy-controlled randomization
        Serially-numbered identical containers
        On-site computer based system with a randomization sequence that is not readable until allocation
        Other approaches sequence to clinicians and patients
    Inferior approaches to concealment of randomization:
        Use of alternation, case record numbers, birth dates or week days
        Open random numbers lists
        Serially numbered envelopes (even sealed opaque envelopes can be subject
        to manipulation)
    Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Reports of Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Economic Studies

Assessment of Internal Validity

Framing

1. Was a well-defined question posed in answerable form?

2. Was a comprehensive description of the competing alternatives given?

3. Are the interventions and populations compared appropriate?

4. Is the study conducted from the societal perspective?

5. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?

2. Are key harms included?

3. Is the best available evidence used to estimate effectiveness?

4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

Costs

1. Are costs and outcomes measured accurately?
2. Are costs and outcomes valued credibly?
3. Are costs and outcomes adjusted for differential timing?
4. Are all appropriate downstream medical costs included?
5. Are charges converted to costs appropriately?
6. Are the best available data used to estimate costs? (like first question)
7. Are all important and relevant costs and outcomes for each alternative identified?

Results

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?
3. How far do study results include all issues of concern to users?

<u>Assessment of External Validity</u>

1. Are the results generalizable to the setting of interest in the review?

Appendix C. Placebo-controlled randomized trials of PPIs (not included)

1. Avner, DL, Movva, R, Nelson, KJ, et al. Comparison of once daily doses of lansoprazole (15, 30, and 60 mg) and placebo in patients with gastric ulcer. American Journal of Gastroenterology 1995;90:1289-94.
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Appendix D. Abstract-only studies (not included)

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Appendix E. Esophagitis grading scales used in randomized controlled trials

Savary-Miller (used in Mulder, 1996, Mee, 1996, and Mulder, 2002):

Grade I: one or more supravestibular, non-confluent reddish spots, with or without exudate.

Grade II: erosive and exudative lesions in the distal esophagus which may be confluent, but not

Grade III: circumferential erosions in the distal esophagus, covered by hemorrhagic and pseudomembranous exudates.

Grade IV: presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia.

Modified Hetzel-Dent (used in Delchier, 2000 and Dekkers, 1999):

Grade 0: Normal mucosa, no abnormalities found

Grade 1: No macroscopic erosions, but presence of erythema, hyperemia, and/or friability of the esophageal mucosa.

Grade 2: Superficial ulceration or erosions involving less than 10% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 3: Superficial ulceration or erosions involving greater than or equal to 10% but less than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 4: Deep ulceraton anywhere in the esophagus or confluent erosion of more than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 5: Stricture, defined as a narrowing of the esophagus that does not allow easy passage of the endoscope without dilation.

Los Angeles Classification(used in Kahrilas, 2000 Richter, 2001, and Castell, 2002):

Not present: No breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present)

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more thatn 5 mm in maximum length, but not continuous between the tops of two mucosal folds.

Grade C: Mucosal breaks that are continuous between the tops of tow or more mucosal folds, but which involve less that 75% of the esophageal circumference.

Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

The presence or absence of strictures, ulcers, and/or Barrett's esophagus much be noted separately, e.g., "Grade B with stricture".

Criteria used in Hatlebakk, 1993:

Grade 1: red streaks or spots along the ridge of the folds in the distal esophagus, covered or not by fibrinous exudate

Grade 2: Broader lesions, each involving the entire width of a fold or coalescing into fields or erythema, covered or not with fibrinous exudates

Grade 3: Stricture or endoscopically visible ulcer in distal esophagus.

Criteria used in Castell, 1996):

Grade 0: normal-appearing mucosa

Grade 1: mucosal edema, hyperemia, and/or friability

Grade 2: one or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus

Grade 3: erosions/ulcerations involving 10-50% of the distal 5 cm of the esophagus or an ulcer 3-5 mm in diameter. In cases of Barrett's esophagus, the area 5 cm proximal to the squamocolmnar juntion was evaluated

Grade 4: multiple erosions involving >50% of the distal 5 cm of the esophagus or a single ulcer > 5mm in diameter.